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The Therapeutic Potential of Carnitine in Cardiovascular Disorders

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Editorial Comment

It is always exhilarating to learn about a new drug that may have potential therapeutic benefits in clinical medicine. It is even more exciting when it may be useful in patients with heart disease.

L-carnitine is a "naturally occurring" compound that "plays an essential role in fatty acid metabolism." Dr. Carl Pepine has reviewed the research findings of this substance in animals and the limited research in human volunteers. He points out that hepatic or renal dysfunction or other catabolic or extraction problems may interfere with carnitine biosynthesis and result in systemic or organ carnitine deficiency. There is research evidence that carnitine may improve the "adverse metabolic effects of myocardial ischemia."

Carnitine has been shown to have a salutary effect in subjects with tachycardia-induced myocardial ischemia associated with coronary artery disease. In acute myocardial infarction, MB-CPK levels were significantly lower in patients given carnitine (40 mg/kg/day) during the first five days of hospitalization.

Dr. Pepine's exhaustive review is filled with important data and interesting findings. Both the patients with acute myocardial infarction and the physicians who treat them need all the help they can get to ensure success of therapy. Cardiologists, as well as primary physicians, should read the present article with eyes and ears tuned for further reports about L-carnitine in the future.

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ABSTRACT

The naturally occurring compound L-carnitine plays an essential role in fatty acid metabolism. It is only by combining with carnitine that the activated long-chain fatty acyl coenzyme A esters in the cytosol are able to be transported to the mitochondrial matrix where β-oxidation occurs. Carnitine also functions in the removal of compounds that are toxic to metabolic pathways. Clinical evidence indicates that carnitine may have a role in the management of a number of cardiovascular disorders. Supplemental administration of carnitine has been shown to reverse cardiomyopathy in patients with systemic carnitine deficiency. Experimental evidence obtained in laboratory animals and the initial clinical experience in man indicate that carnitine may also have potential in the management of both chronic and acute ischemic syndromes. Peripheral vascular disease, congestive heart failure, cardiac arrhythmias, and anthracycline-induced cardiotoxicity are other cardiovascular conditions that may benefit from carnitine administration, although at this time data on the use of carnitine for these indications are very preliminary.

INTRODUCTION

Carnitine is a naturally occurring compound in the body, found in high concentration in myocardium and muscular tissue. This substance is an essential factor in the transport of long-chain fatty acids from the cytoplasm to the interior of the mitochondrion, where β-oxidation takes place, as well as in the removal of toxic compounds. Defective carnitine biosynthesis may occur as a result of defects in either liver or kidney function, increased catabolism, or the inability of tissues to extract carnitine from the blood and retain it. These conditions may occur in many pathologic states or as the result of aging and lead to either systemic or organ carnitine deficiency. As a consequence, energy availability is decreased and there is a pathologic accumulation, essentially in the cytoplasm, of free fatty acids, which is highly toxic to cell membranes. Accordingly, the purpose of this article is to critically examine the role of carnitine in cardiovascular

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disorders in order to assess its therapeutic potential.

Clinically Relevant Biochemistry of Carnitine

Before discussing the pharmacologic and pharmacokinetic properties and therapeutic potential of carnitine, a review of its biochemistry is relevant. The structural formula of L-carnitine, or 3-hydroxy-4-N-trimethylaminobutyric acid, is shown in Figure 1. Although a racemic mixture of carnitine (DL-carnitine) has been produced synthetically, it is only the L-isomer that is metabolically active.

The principal function of carnitine is to facilitate transport of long-chain fatty acids present in the cytosol across the inner mitochondrial membrane to the mitochondrial matrix, the site of β-oxidation.[1-3] The mitochondrial membrane is normally impermeable to the activated coenzyme A (CoA) esters formed in the cytosol by the action of fatty acyl-CoA synthetase. In order to enter the mitochondria, acyl-CoA must combine with L-carnitine to form acylcarnitine, which is capable of penetrating the mitochondrial membrane (Figure 2). This reaction is catalyzed by an enzyme known as carnitine acyltransferase I. Another enzyme, carnitine translocase, subsequently mediates the transport of acylcarnitine across the inner mitochondrial membrane. Once acylcarnitine has entered the mitochondrial matrix, carnitine acyltransferase II facilitates regeneration of acyl-CoA and free carnitine. Acyl-CoA then undergoes β-oxidation to acetyl-CoA, which enters the Krebs or citric acid cycle, the sequence of reactions by which energy production occurs. Carnitine is returned to the cytosol where it can again react with acyl-CoA. Thus, the CoA derivatives of long-chain fatty acids become available for β-oxidation with expenditure of energy as an adenosine triphosphate (ATP) molecule; toxic substances may also be removed by this process.[4,5]

Pharmacologic Effects of Carnitine

Animal Pharmacology

Hemodynamic effects. Evaluation of the hemodynamic effects of carnitine in laboratory animals has provided evidence of both a positive inotropic effect and a direct coronary vasodilatory effect. Anesthetized, closed-chest dogs given an intravenous infusion of 80 mg/kg/min of L-carnitine for eight minutes demonstrated a 17% decrease in heart rate, a 20% increase in aortic and left ventricular pressures, and a 35% increase in peak positive left ventricular dP/dt.[6] The

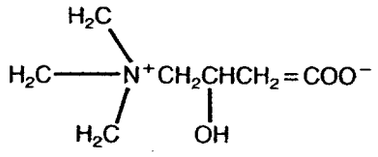

Figure 1. Chemical structure of L-carnitine.

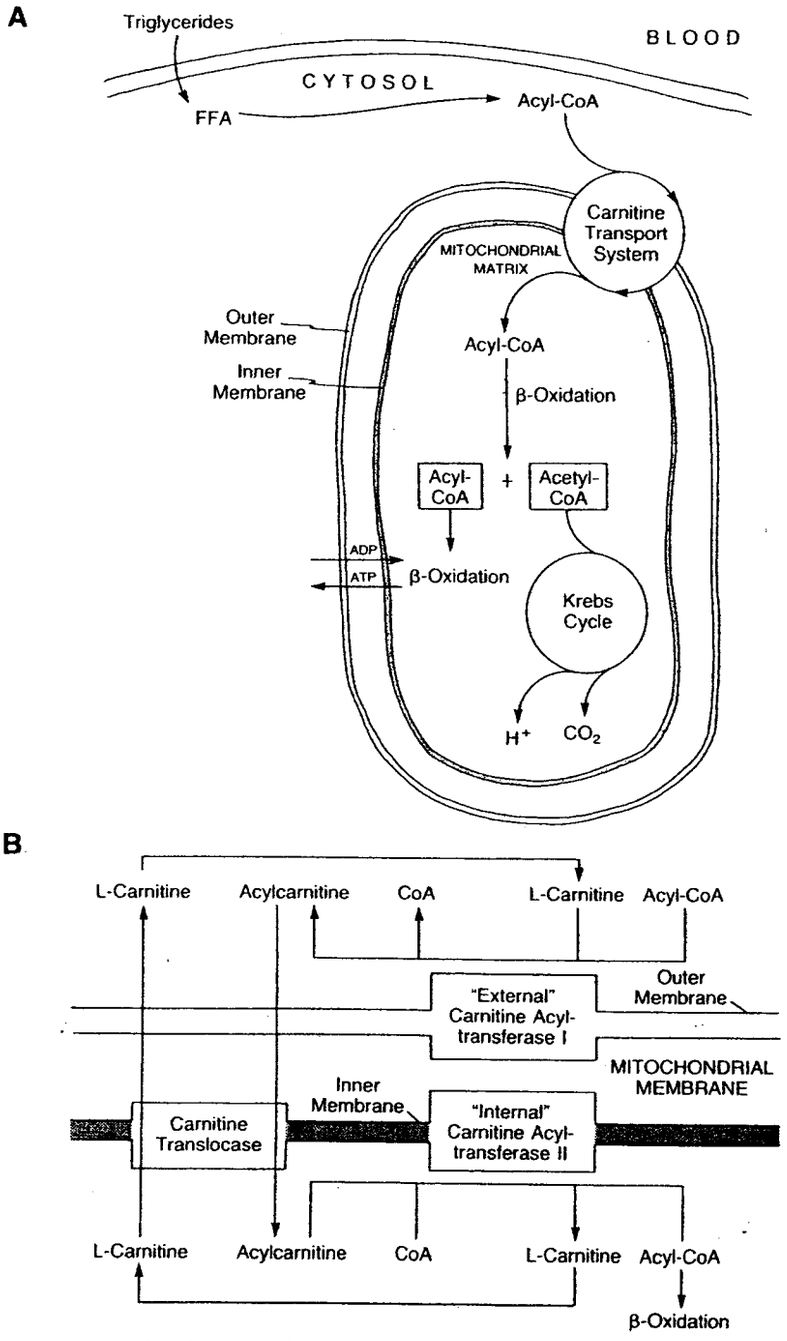

Figure 2. Steps involved in (*A*) fatty acid oxidation and (*B*) carnitine-mediated transport of fatty acids across the mitochondrial membrane. Long-chain fatty acids are transported as acyl-CoA derivatives in all organs and therefore require carnitine. Although medium-chain fatty acids do not require carnitine for transport in the liver, they may also require carnitine for transport in heart and skeletal muscle. (FFA = free fatty acids; CoA = coenzyme A; ADP = adenosine diphosphate; ATP = adenosine triphosphate.)

positive inotropic activity of L-carnitine seen in these animals was accompanied by a 60% rise in coronary blood flow and a 25% reduction in coronary vascular resistance.

A separate investigation examined the effects of intravenous infusion of DL-carnitine at rates of 10 to 70 mg/kg/min on cardiac and peripheral vessel hemodynamic parameters in anesthetized, open-chest dogs.[7] Carnitine infusion rates of 20 mg/kg/min and lower elicited a minimal hemodynamic response, but rates of 30 and 40 mg/kg/min produced a mild positive inotropic effect and a marked vasodilatory effect. These responses were manifested by reductions in coronary, pulmonary, and systemic vascular resistances, widened pulse pressures in these vascular beds, and increases in left circumflex coronary blood flow and mean aortic flow. At higher infusion rates, the positive inotropic effect of carnitine became more pronounced. The 60-mg/kg/min infusion rate was associated with a doubling of stroke volume, a nearly threefold increase in left ventricular end-diastolic pressure (LVEDP), a rise in left ventricular dP/dt_{max}, and a 38% increase in left ventricular contractile force. Failure of either propranolol or reserpine to reverse changes induced by carnitine infusion indicated that the hemodynamic effects seen in these animals were not mediated by catecholamines.

Metabolic effects. Other experimental evidence suggests that carnitine improves the adverse metabolic changes associated with myocardial ischemia. Intravenous administration of L-carnitine to open-chest, anesthetized dogs prior to coronary artery ligation attenuated the decrease in free carnitine and increases both in long-chain acylcarnitine and in long-chain acyl-CoA observed in the ischemic area of hearts from untreated animals.[8] In addition, ATP concentration in the ischemic region was significantly higher in carnitine-treated animals than in controls. Effects achieved with intracoronary infusion of L-carnitine following the onset of ischemia included increases in tissue levels of free carnitine, acetylcarnitine, creatine phosphate, and ATP, and a decrease in long-chain acyl-CoA esters.[9,10]

Human Pharmacology

Hemodynamic effects. The positive inotropic activity of carnitine observed in laboratory animals has also been detected in man. This effect, however, appears to be much more pronounced in patients with evidence of ischemic heart disease than in normal individuals.

An intravenous dose of 40 mg/kg of L-carnitine administered to healthy volunteers over a period of two minutes produced only modest variations in heart rate and arterial pressure.[11] Likewise, insignificant alterations in the pre-ejection period (PEP), left ventricular ejection time (LVET), and the PEP/LVET ratio, and no marked changes in echocardiographic indices of cardiac performance were seen. When these same workers studied ten patients with presumed coronary artery disease, manifest as myocardial infarction or angina pectoris, only slight changes in arterial pressure and heart rate were observed during carnitine infusion. At ten minutes after the infusion, a 10% decrease in PEP was noted in these patients, and a 3% reduction was apparent 45 minutes postinfusion. LVET

increased slightly over baseline values throughout the infusion period. A maximal decrease in the PEP/LVET ratio of approximately 15% occurred at ten minutes after carnitine infusion. A 10% reduction in this ratio persisted 45 minutes after completion of the infusion. Echocardiographic examination of these patients showed significant increases in left ventricular wall motion after 40 mg/kg given intravenously over two minutes.

Giordano and associates[12] reported a similar beneficial effect on cardiac performance after a more prolonged period of carnitine administration to 18 patients with angina pectoris and mild heart failure symptoms. After ten days of treatment with 2 gm/day of intravenous carnitine, a significant increase in PEP and a significant reduction in LVET were observed as compared with baseline values. These changes resulted in a significant decrease in the PEP/LVET ratio.

The hemodynamic effects of carnitine during tachycardia stress, induced by either atrial pacing or exercise, have also been examined in patients with angina and coronary artery disease.[13] Changes in heart rate, LVEDP or ejection fraction, and left ventricular systolic pressure in four patients treated with 40 mg/kg of carnitine did not differ significantly from changes noted in seven patients who received saline. No significant changes were seen in systolic pressure or maximal pacing heart rate, but carnitine appeared to reduce the pacing-induced increase in LVEDP. Metabolic findings in these patients are reviewed below.

Metabolic effects. Observations during rapid atrial pacing of patients with angina due to coronary artery disease indicate that carnitine has a favorable effect on myocardial metabolism of both free fatty acids and lactate during tachycardia stress.[13-16] Tachycardia stress prior to carnitine administration was associated with reduced myocardial lactate extraction. In one study,[13,14] intravenous infusion of L-carnitine prior to a second tachycardia period resulted in conversion of lactate production to extraction. A second group of investigators also reported an increase in myocardial lactate extraction following treatment with DL-carnitine.[15] In a third study,[16] the reduction in lactate extraction caused by tachycardia stress decreased significantly after large doses of carnitine (140 mg/kg), given as an extravascular bolus, as compared with the same patients prior to carnitine administration and placebo-treated patients. Additionally, ST segment depression was reduced during tachycardia stress after carnitine compared to tachycardia stress before either its administration or placebo.

Pharmacokinetics of Carnitine in Man

Because carnitine occurs endogenously, its pharmacokinetic properties can only be studied under very carefully controlled conditions that take into account dietary intake and baseline serum and urine levels. The need for such considerations may explain the paucity of information on the pharmacokinetic behavior of exogenously administered carnitine.

After Intravenous Administration

The data that are available show that serum levels of carnitine rise rapidly following intravenous administration of

either the L-isomer or the racemic mixture.[17-19] In one study,[17] healthy volunteers given an intravenous dose of 40 mg/kg of L-carnitine demonstrated a peak serum carnitine level of 1,612.3 μM, a value 36 times higher than the baseline concentration. The initial increase in serum carnitine that occurs after intravenous administration is followed by a rapid decline. Serum carnitine concentrations generally return to near baseline levels approximately 12 hours postinfusion.

Welling and coworkers[18] used a two-compartment model to describe the distribution of L-carnitine in adult men after intravenous doses ranging between 40 and 60 mg/kg of DL-carnitine. Initially, L-carnitine was rapidly distributed into a volume approximately 20% of body weight. At steady state, the L-carnitine distribution volume was 30% of body weight, a value consistent with extensive distribution into the extracellular fluid. The half-life of the distribution phase was approximately 0.5 hour, and that of the terminal beta phase was about two to three hours.

Serum concentrations of carnitine detected by Uematsu and colleagues[17] in healthy subjects given intravenous doses ranging from 20 to 60 mg/kg of L-carnitine fitted better to a three-compartment open model. The volume of distribution of the central compartment ranged from 0.11 to 0.20 L/kg and again corresponded to extracellular fluid volume. Carnitine was subsequently distributed into two peripheral compartments. The half-life of the gamma phase of disappearance of carnitine from the serum ranged from 10 to 23 hours.

Intravenously administered carnitine is eliminated principally in the urine.[17-19] Mean 24-hour urinary recovery reported by Uematsu and coworkers[17] after intravenous L-carnitine in doses ranging from 20 to 60 mg/kg was 83.5%. Similar urinary excretion levels have been noted by other investigators.[18,19] The major fraction of carnitine appears to be excreted unchanged.[18]

After Oral Administration

The rise in serum levels of carnitine after oral administration of 2 or 6 gm of L-carnitine was more gradual and the peak concentrations achieved were much lower than after intravenous doses.[19] Maximal serum concentrations occurred between 3 and 9 hours after a 2-gm dose and 2.5 to 7 hours after a 6-gm dose. Only 1,021 μmol of carnitine, or 8% of the administered dose, was recovered in the urine within 24 hours after an oral dose of 2 gm of L-carnitine. After the 6-gm dose, urinary recovery was 1,580 μmol, only 4% of the dose.

Bioavailability of the 2-gm dose of L-carnitine ranged from 9% to 25%, whereas bioavailability of the 6-gm dose was only 4% to 10%. Furthermore, the area under the time-concentration curve did not differ significantly between the two dose levels. These findings suggested saturation of carnitine absorption at the 2-gm dose level.

Renal Function and Carnitine Pharmacokinetics

Although little is known about the impact of disease on the pharmacokinetic behavior of carnitine, the influence of renal function on plasma and urinary concentrations of total, free, short-chain, and acetyl-L-carnitine after oral doses of 1,500 or 3,000 mg of acetyl-L-carnitine

has been examined.[20] Participants in this study included six subjects with normal renal function and 18 patients with varying degrees of renal impairment.

Prior to acetyl-L-carnitine administration, predose levels of all four substances studied were found to be inversely related to creatinine clearance. Levels in patients with renal impairment, however, did not differ markedly from those in individuals with normal renal function until the creatinine clearance fell to below 40 ml/min. Small increases in plasma concentrations of total, free, short-chain, and acetyl-L-carnitine, which tended to be somewhat greater in patients with more severe renal impairment, were noted following the acetyl-L-carnitine dose. Doubling of the acetyl-L-carnitine dose from 1,500 to 3,000 mg had little effect on peak plasma concentrations.

Urinary elimination of all four substances declined with progressive renal impairment. Increases in renal elimination and renal clearance, however, occurred at the higher acetyl-L-carnitine dose level, suggesting that the mechanism for maintaining the homeostatic equilibrium of L-carnitine and related substances was preserved in patients with renal dysfunction.

Tolerability of Carnitine

Because L-carnitine is an endogenous substance, exogenous administration would be expected to cause few, if any, serious adverse effects. Clinical experience with L-carnitine in the treatment of primary carnitine deficiency and its use in clinical trials in patients with myocardial ischemia, peripheral vascular disease, and various other cardiovascular disorders have supported this expectation. Adverse reactions that have been reported have consisted primarily of mild gastrointestinal complaints, such as transient nausea and vomiting, abdominal cramps, and diarrhea. These effects usually resolve with a reduction in the carnitine dosage.

Carnitine Formulations and Dosage

Carnitine is supplied as a prescription product, in tablet or solution form, for oral administration and as an experimental intravenous formulation (currently requiring an investigational new drug application for use). The recommended oral dosage for treatment of primary systemic carnitine deficiency in adults is 990 mg BID or TID. Infants and children should receive 50 to 100 mg/kg/day in divided doses, up to a maximum of 3 gm/day. The optimal dosage of carnitine for management of other cardiovascular disorders has not yet been established. Two other preparations, acetylcarnitine and propionyl carnitine, are in use in Europe. The acetylcarnitine was developed for transport into the brain, and propionyl carnitine for transport into myocardium.

In the United States, carnitine is also available as a nutritional food supplement or "health food." Such formulations, however, have not been designated as safe and effective by the Food and Drug Administration. Furthermore, the manufacturers of these products are not required to comply with the current good manufacturing practice regulations that set forth minimum standards for the manufacturing, processing, and packaging of drugs. Therefore, use of prescription formulations of carnitine is recommended only for the treatment of disease.

CARNITINE IN MANAGEMENT OF CARDIOMYOPATHY DUE TO SYSTEMIC CARNITINE DEFICIENCY

Primary carnitine deficiency syndromes have been classified as systemic or myopathic. The myopathic form is associated with normal serum levels of carnitine but depressed skeletal muscle concentrations and is manifested principally by progressive weakness of the skeletal muscles. In systemic carnitine deficiency, both serum and tissue carnitine levels are abnormally low and multisystem involvement is common. Cardiomyopathy is the predominant cardiac feature of the systemic syndrome. Other signs and symptoms may include encephalopathy, seizures, and other neurologic abnormalities; hepatomegaly; and skeletal muscle weakness. Histologic examination of myocardial, skeletal-muscle, or hepatic tissues from patients with systemic carnitine deficiency has shown increased lipid deposition and abnormal aggregated mitochondria. Metabolic abnormalities commonly observed in afflicted patients include hypoglycemia, hyperammonemia, and recurrent episodes of acidosis.

A rapid, dramatic clinical response characterized by improvement in cardiac function has been noted in patients with systemic carnitine deficiency treated with supplemental carnitine (Table I).[21-26] In one 5½-year-old boy, left ventricular ejection fraction increased from 39% to 75% after only one month of treatment with L-carnitine 990 mg TID.[22] By the end of two months, the cardiothoracic ratio in this child had decreased to 0.57 from 0.72 prior to treatment. Other signs of improvement in cardiac function in carnitine-treated patients include decreases in left-ventricular-chamber dimensions. Some investigators have also reported a reduction in the amplitude of abnormally high T-waves recorded in the precordial leads.[22,26] In the patient treated by Waber and associates,[22] discontinuation of digitalis and diuretic therapy became possible after initiation of carnitine therapy. These data provide strong evidence to suggest that carnitine therapy may reverse the cardiac manifestation of carnitine deficiency.

Improvements in the noncardiac manifestations of systemic carnitine deficiency, including an increase in muscle strength, disappearance of neurologic abnormalities, and regression of hepatomegaly, have also occurred in response to carnitine supplementation. In addition, carnitine therapy has been associated with improvement in disease-related metabolic derangements.

CARNITINE IN MANAGEMENT OF MYOCARDIAL ISCHEMIA

A reduction in blood supply to the myocardium causes a decrease in the production of energy by the oxygen-dependent pathway of fatty acid metabolism. This decline in fatty acid oxidation leads to accumulation of long-chain acyl-CoA esters, which may aggravate ischemic damage by a number of mechanisms. For example, at high concentrations acyl-CoA esters inhibit their own oxidation.[1] These substances can also have an inhibitory effect on fatty acyl-CoA synthetase, the enzyme responsible for the activation of long-chain fatty acids.[27] More importantly, however, acyl-CoA esters block the activity of adenine nucleotide translocase, which mediates the exchange of ATP for adenosine diphos-

phate across the mitochondrial membrane.[1,27] As a result, any ATP that may be produced due to a residual collateral blood supply becomes sequestered in the mitochondria. The decrease in cytosol ATP concentration due to the combination of a decrease in oxidative metabolism and the inhibition of adenine nucleotide translocase stimulates the activity of phosphofructokinase, which normally regulates the rate of aerobic glycolysis, thereby leading to the production of lactate.[13]

Decreased levels of free carnitine have been detected in myocardial tissue from laboratory animals with experimentally induced ischemia[8,9] and in the necrotic zone of specimens of infarcted myocardium obtained from humans at autopsy.[28] This depression in the myocardial carnitine concentration can be expected to limit the transport of acyl-CoA esters across the mitochondrial membrane (Figure 2). Under normal conditions, carnitine also indirectly stimulates pyruvate dehydrogenase by decreasing the acetyl-CoA/CoA ratio.[27] The carnitine deficiency associated with myocardial ischemia, however, results in an increase in

Table I. Manifestations of cardiac improvement in patients with systemic carnitine deficiency treated with oral carnitine.

Authors	Number of Patients	Carnitine Form and Dose	Response
Ino et al[21]	8	L-carnitine, 100-250 mg TID or QID	↓CTR; improvement in ST-T wave abnormalities; ↑FS; reduction in LV size
Waber et al[22]	1	L-carnitine, 990 mg TID	↓CTR; ↑LVEF; ↓T-wave amplitude
Matsuishi et al[23]	2	DL-carnitine, 3 gm/day	↓CTR; ↑LVEF
Chapoy et al[24]	1	DL-carnitine, 4 gm/day; L-carnitine, 2 mg/day	↓CTR; ↓LV chamber dimensions; ↑FS; ↑VCF; ↓LV wall thickness
Kerr et al[25]	1	L-carnitine, 50 mg/kg/day	Improvement in cardiac function
Tripp et al[26]	1	L-carnitine, 1 gm TID	↓NYHA class; ↓left atrial and LV chamber dimensions; ↑FS; ↑work capacity; ↓T-wave amplitude
Total	14	Range, 100 mg TID to 4 gm/day	↓CTR; ↓LV size; ↑wall motion

CTR = cardiothoracic ratio; LV = left ventricular; LVEF = LV ejection fraction; FS = fractional shortening; NYHA = New York Heart Association; QID = four times daily; TID = three times daily; VCF = velocity of circumferential fiber shortening.

this ratio, which leads to the inhibition of pyruvate dehydrogenase and the conversion of pyruvate to lactate rather than its entry into the citric acid cycle.

It has been suggested that exogenous administration of carnitine may reduce the elevated levels of acyl-CoA esters associated with ischemia by promoting the formation of acylcarnitine, which is believed to be less harmful to the myocardial cells. Carnitine might also accelerate the rate of glycolysis by stimulating pyruvate dehydrogenase, thereby reversing the metabolic acidosis that may occur during ischemia.

As mentioned in the discussion of the metabolic effects of carnitine, administration of exogenous carnitine to laboratory animals prior to or during ischemia increases tissue levels of free carnitine and decreases concentrations of long-chain acyl-CoA esters.[8,9] In addition, a reduction in ST-segment deviation, which is generally regarded as an index of the extent of myocardial damage, has also been observed in carnitine-treated animals.[9,10] Treatment with DL-carnitine has also improved hemodynamic performance in free fatty acid–supplemented ischemic swine hearts.[29] The favorable response to carnitine seen in these experimental studies has led to the evaluation of carnitine for the management of various ischemic syndromes in man.

Effects of Carnitine in Patients with Transient Myocardial Ischemia

Effects on Tachycardia Tolerance

Several studies have examined the effect of carnitine on the response to atrial-pacing-induced tachycardia in patients with ischemia attributable to coronary artery disease.[13-16] Administration of DL- or L-carnitine to such patients was consistently associated with a favorable effect, although findings varied somewhat among the individual investigations (Table II). Thomsen and colleagues[15] noted a significant improvement in the duration that tachycardia was tolerated as well as significant increases in maximal heart rate and rate-pressure product after administration of either 20 or 40 mg/kg of DL-carnitine. The tachycardia-stress-induced increase in LVEDP was also reduced in carnitine-treated patients. Ferrari and associates[13,14] also noted a reduction in LVEDP after intravenous infusion of 40 mg/kg of L-carnitine to patients with ischemic heart disease. In a study conducted by Reforzo and coworkers,[16] carnitine diminished the magnitude of ischemic-type ST-segment depression that occurred during tachycardia stress.

All three groups of investigators noted improvement in myocardial lactate metabolism after carnitine administration. As discussed above, carnitine caused a significant increase in myocardial lactate extraction during tachycardia stress. Ferrari and associates[13,14] also reported a significant reduction in the arterial free fatty acid concentration at rest in patients treated with L-carnitine. The myocardial A-V difference for free fatty acids, however, was maintained, suggesting an increase in myocardial free fatty acid extraction.

Effect on Exercise Tolerance

Evaluations of the effect of carnitine on exercise tolerance in symptomatic pa-

tients with coronary artery disease have demonstrated improvements both in exercise capacity and electrocardiographic manifestations of ischemia (Table II).[30-33] Increases were noted in overall exercise time[30,31] and in the time to the onset of ischemia.[30] Maximal work load increased and the degree of ST-segment depression at maximal work load declined.[31-33] Echocardiographic evaluation of the patients enrolled in one of these studies[33] suggested improvement in left ventricular function after 30 days of treatment with 2 gm/day of carnitine.

Table II. Effect of carnitine on pacing and exercise tolerance in patients with coronary heart disease.

Authors	Number of Patients	Carnitine Form and Dose	Response
Effect on Pacing Tachycardia Tolerance			
Ferrari et al[13,14]	11	L-carnitine, IV, 40 mg/kg	↓LVEDP; improved myocardial metabolism
Thomsen et al[15]	11	DL-carnitine, IV, 20 or 40 mg/kg	↑maximal HR; ↑maximal RPP; ↑duration of pacing; improved myocardial metabolism
Reforzo et al[16]	19	L-carnitine, extravascular bolus, 140 mg/kg	↓ST depression; improved myocardial metabolism
Effect on Exercise Tolerance			
Kawikawa et al[30]	12	L-carnitine, oral, 900 mg/day, 12 weeks	↑exercise time; ↑time to onset of ST depression
Kosolcharoen et al[31]	18	DL-carnitine, IV, 40 mg/kg, single dose	↓ST depression during exercise and recovery; ↑exercise time to angina; slower rise in HR and RPP
Canale et al[32]	16	L-carnitine, oral, 3 gm/day, 30 days	↑work load; ↓ST depression; ↓angina; echocardiographic improvement in LVF
Cherchi et al[33]	44	L-carnitine, oral, 1 gm BID, 4 weeks	↑exercise work load; ↓ST depression at maximal work load and maximal common work load; ↑work load to angina

BID = twice daily; HR = heart rate; IV = intravenous; RPP = rate-pressure product; LVEDP = left ventricular end diastolic pressure; LVF = left ventricular function.

Effect on Symptoms

Symptomatic improvement has also occurred in response to carnitine. Orlando and Rusconi[34] used 2 mg of carnitine BID or TID to treat 30 elderly patients with chronic, stable ischemic heart disease. After two months of carnitine administration, these patients reported decreases in palpitations, in asthenia, and in precordial pain. In addition, New York Heart Association (NYHA) functional class improved in four patients, and pretreatment electrocardiographic repolarization abnormalities improved or normalized in six patients. Five others demonstrated a 12% to 20% improvement in left ventricular shortening fraction, assessed by echocardiography.

The data are limited but suggest that some improvement may occur in patients with coronary artery disease who receive carnitine. Clearly, more data from controlled clinical trials are needed.

Effects of Carnitine in Patients with Acute Myocardial Infarction

The limited data that are available also suggest that carnitine may reduce the extent of necrosis associated with acute myocardial infarction. Rebuzzi and associates[35] used L-carnitine as an adjunct to traditional therapy in 12 patients with Q-wave myocardial infarction, all of whom were hospitalized within eight hours of the onset of chest pain. The L-carnitine regimen consisted of 40 mg/kg/day for the first five days of hospitalization. The next ten patients, who received standard therapy alone, served as a control group. It should be noted, however, that these patients were not randomly assigned to their treatment groups.

Both the total MB-CPK* release and maximum release during the study observation period were significantly lower in carnitine-treated patients than in the control group. Carnitine was also associated with a lower total release time and a lower rate of MB-CPK release as compared with values seen in control patients, although differences between the two groups did not reach statistical significance. The possible antiarrhythmic activity of carnitine (discussed below) was mentioned but not evaluated.

Effects of Carnitine in Patients with Other Ischemic Syndromes

Effects in Aortocoronary Bypass Surgery

Based upon favorable effects in animal models with ischemia,[8-10] preoperative administration of carnitine was used in an attempt to improve the metabolic derangements associated with ischemia in patients undergoing aortocoronary bypass surgery. Bohles and coworkers[36] evaluated the effects of supplemental carnitine in 20 patients undergoing this surgical procedure. L-carnitine was given orally at a dose of 1 gm/day for two days prior to surgery and then intravenously at a dose of 0.5 gm immediately prior to the operation. Findings in the study population were compared with those in 20 patients who did not receive carnitine.

Although the total myocardial carnitine concentration in the two groups was similar, myocardial free carnitine increased and long-chain acylcarnitine decreased significantly in the patients who received supplemental carnitine. Carnitine-treated patients also demonstrated significantly

*MB isoenzyme of creatinine phosphokinase.

higher myocardial ATP concentrations than those not receiving carnitine. The higher ATP values in the carnitine treatment group corresponded with lower myocardial lactate concentrations.

Effects in Peripheral Vascular Disease

Effects in vasospastic syndromes. Patients with peripheral vasospastic syndromes may also benefit from carnitine therapy. Administration of 2 gm/day of carnitine for three days to 16 patients with vasospastic disturbances of the upper extremities resulted in a reduction in the number of vasospastic attacks.[37] These patients also demonstrated plethysmographic improvement, which correlated with the decrease in vasospastic episodes.

Effects in atherosclerotic peripheral vascular disease. Oxidation of fatty acids is also an important source of energy for skeletal muscle. In patients with peripheral vascular obstruction, however, skeletal-muscle oxidative metabolism may be impaired, resulting in progression of symptoms even during normal daily activities. Such metabolic impairment is reflected by significant elevation in plasma acylcarnitines detected in patients with peripheral vascular disease after a relatively short duration of low-level exercise.[38] In normal subjects, increases in plasma concentrations of acylcarnitines are generally seen only with maximal exertion or prolonged exercise. The improvement in exercise performance achieved with exercise conditioning in patients with peripheral arterial disease is accompanied by a reduction in plasma concentrations of short-chain acylcarnitines, a finding that suggests improvement in skeletal-muscle oxidative metabolism.[39]

Few studies have examined the effect of carnitine in patients with peripheral vascular disease, but the data that are available are promising. In one double-blind, crossover trial,[40] 20 patients with peripheral vascular disease were treated alternately with either placebo or oral L-carnitine 2 gm BID for three weeks. The absolute walking capacity achieved by these patients after carnitine therapy was 75% greater than the walking capacity observed after placebo administration. Walking time increased by 67% in a separate series of eight patients given a short intravenous course of L-carnitine. Carnitine also reduced complaints of paresthesias, tiredness, pain during walking, and coldness, whereas placebo had only a slight effect on these subjective symptoms.

General and regional hemodynamics did not change after carnitine given parenterally, suggesting that the beneficial effects on walking distance were more likely due to a metabolic rather than a hemodynamic mechanism. In fact, carnitine did inhibit the increases in both popliteal venous lactate concentration and lactate/pyruvate ratio seen with placebo both during exercise and in the postexercise recovery period. These findings were believed to be related to stimulation of pyruvate dehydrogenase resulting from a carnitine-induced reduction in the acetyl-CoA/CoA ratio. This effect would be expected to cause a decrease in the formation of lactate and an increase in energy production due to pyruvate oxidation. The improvement in the hyperemic response to temporary ischemia noted in patients with peripheral vascular disease after intravenous administration

of L-carnitine may also reflect the metabolic effects of carnitine.[41] The release of adenosine due to increased utilization of ATP may account for this improvement in functional circulatory reserve.

An increase in walking capacity has also been noted in patients with intermittent claudication treated with acetylcarnitine.[42] Parenteral administration of 500 mg/day of acetylcarnitine for 30 days, followed by oral therapy at the same dose three times daily, increased walking distance in 80% of 80 patients evaluated. The percentage improvement in this population ranged from 20% to 40%. Again, more data are needed to support these very encouraging results.

EFFECT OF CARNITINE IN OTHER CARDIOVASCULAR DISORDERS

Heart Failure and Left Ventricular Dysfunction

A significant reduction in free carnitine and significant increases in short- and long-chain acylcarnitine have been detected in papillary muscle biopsy specimens from patients with chronic heart failure undergoing valve replacement.[43] A reduced carnitine concentration has also been reported in endomyocardial biopsies from patients with less severe congestive heart failure secondary either to dilated cardiomyopathy or to coronary artery, valvular, or hypertensive heart disease.[44] These findings suggested the possibility that patients with congestive heart failure might benefit from carnitine supplementation.

The possible therapeutic value of carnitine for this indication was evaluated in an Italian study involving 38 elderly patients with congestive heart failure secondary to ischemia or hypertensive heart disease.[45] All of these patients received traditional therapy with digitalis and diuretics and, when necessary, antiarrhythmic agents. Twenty-one patients were also treated with oral L-carnitine at a dose of 1 gm twice daily for 45 days. The other 17 received placebo.

Both groups demonstrated similar improvement in subjective and objective clinical parameters and NYHA functional class. Echocardiographic measures of left ventricular wall motion and size also indicated a favorable effect. Electrocardiographic changes suggesting ischemia were reduced in both groups, but improvement was more marked in patients who received L-carnitine. The L-carnitine-treated group also experienced a reduction in the incidence of cardiac arrhythmias, particularly ventricular extrasystoles, and a more marked decrease in digoxin requirements. These preliminary observations appear to justify the further assessment of the role of L-carnitine as adjunctive therapy in patients with congestive heart failure.

Diphtheritic Guinea Pig Myocarditis

A decrease in fatty acid oxidation related to myocardial carnitine depletion may contribute to the myocarditis associated with diphtheria. Addition of L-carnitine to the perfusate of isolated, intact, perfused hearts from diphtheritic guinea pigs increased the previously depressed rate of palmitate oxidation to a level almost identical to that found in normal hearts.[46] The rise in myocardial levels of total carnitine and the free, soluble, and insoluble carnitine subfractions noted in diphtheritic guinea pigs after intraperitoneal administration of

25 gm L-carnitine BID for four days suggests that the improvement in fatty acid oxidation seen in the perfused hearts was related to the repletion of myocardial carnitine. L-carnitine has also been found to decrease mortality and prolong survival in guinea pigs given diphtheria toxin and to improve left ventricular function and cardiac output in diphtheritic dogs.[47] The relevance of this animal model with heart failure to humans with heart failure is difficult to determine. Nevertheless, these results do suggest that metabolic support may improve left ventricular function.

Carnitine in the Prevention of Cardiac Arrhythmias

The fatty acid esters that accumulate as a result of impairment of fatty acid oxidation in carnitine-deficient states may be arrhythmogenic under certain conditions. The reduction in the threshold for electrically induced atrial fibrillation noted in intact cats after intravenous administration of carnitine[48] suggested that carnitine may be useful in preventing arrhythmias associated with carnitine deficiencies in man.

The antiarrhythmic potential of carnitine has been evaluated in a limited number of clinical trials. One double-blind study[49] examined the effect of carnitine on ventricular arrhythmias in patients with acute myocardial infarction. The 56 subjects received infusions of 100 mg/kg of L-carnitine or placebo every 12 hours for a total of 36 hours. On the second day of the study, premature ventricular beats (PVBs)/hour, hours with multifocal PVBs, hours with paired PVBs, and the number of episodes of ventricular tachycardia were all significantly lower in the 28 patients treated with L-carnitine than in the 28 receiving placebo. These antiarrhythmic effects were accompanied by significant increases in serum and urinary levels of free carnitine and short- and long-chain carnitine esters during the first 48 hours after admission to the coronary unit.

Loss of carnitine into the dialysate may contribute to the development of cardiac arrhythmias in patients with renal failure undergoing hemodialysis. Suzuki and associates[50] reported a significant reduction in the frequency of ventricular arrhythmias in eight hemodialysis patients treated with 2 mg/day of carnitine. After four weeks of carnitine administration, the overall frequency of premature ventricular beats in these patients was reduced by 48%. A greater than 90% reduction was seen in three of the seven patients evaluated at this time. After eight weeks, the frequency of premature ventricular beats was reduced by 60%, with a greater than 90% reduction apparent in five of eight patients evaluated. Carnitine therapy also resulted in an increase in plasma carnitine, which was below the normal level at the start of treatment, and a reduction in the peak plasma free fatty acid concentration seen 20 minutes after the start of hemodialysis.

Effect of Carnitine on Anthracycline-Induced Cardiotoxicity

The development of cardiotoxicity has limited the long-term use of the antineoplastic anthracycline antibiotics daunorubicin and doxorubicin. Early manifestations of the cardiotoxic effects of these agents include transient, reversible tachycardia, constriction of the coronary

arteries, and elevated serum levels of the MB-CPK isoenzyme. In the later phase of anthracycline-induced cardiotoxicity, cellular damage is accompanied by congestive heart failure and electrocardiographic abnormalities. These adverse effects are believed to be attributable to the accumulation of free fatty acids and long-chain acyl-CoA esters and the disruption of cellular calcium homeostasis.

Preliminary evidence suggests that carnitine may have potential in the prevention of anthracycline-induced cardiotoxicity. In one early study, eight cancer patients undergoing treatment with doxorubicin or daunorubicin were given 3 gm/day of oral L-carnitine for two days before and two days after chemotherapy.[51] No significant increases in serum MB-CPK levels were observed in any of these patients after anthracycline administration, and some actually demonstrated a significant decrease.

De Leonardis and associates[52] evaluated the cardioprotective effect of carnitine in nine patients receiving anthracycline derivatives for the treatment of solid or proliferative diseases. The regimen used by these investigators consisted of 3 gm/day of L-carnitine orally for three days before and after anthracycline administration and 1 gm intravenously on the day of anthracycline therapy. Again, no significant increase in MB-CPK serum levels occurred after administration of either doxorubicin or daunorubicin given in combination with L-carnitine. The maximum velocity of circumferential fiber shortening (VCF_{max}), assessed by echocardiography, fell to below the normal value in one patient who received the highest cumulative dose of 490 mg/m^2 of doxorubicin, but anthracycline therapy had no significant effect on VCF_{max} in any of the other eight patients.

This same group of investigators[53] subsequently reported no significant reduction in VCF_{max} in five cancer patients after six cycles of treatment with doxorubicin plus the same carnitine regimen used in the previous study. In contrast, VCF_{max} was significantly reduced in four patients who had received four cycles of chemotherapy with doxorubicin alone. These results are most encouraging and deserve further attention because this is usually a progressive disease, for which the only treatment, at present, is cardiac transplantation.

SUMMARY

Place of Carnitine in the Management of Cardiovascular Disorders

Clinical experience has shown that supplementation with L-carnitine can improve myocardial function in patients with primary systemic carnitine deficiencies. 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. The fact that carnitine has a different mechanism of action than the drugs traditionally used for the management of ischemia could make carnitine a particularly attractive choice for adjunctive therapy in this disorder. Preliminary data also suggest that carnitine, used in conjunction with standard therapy, may also reduce cellular injury due to acute myocardial infarction.

Information available at this time, although limited, also indicates that

carnitine may have a role in the management of various other cardiovascular disorders as well. Improvement in walking time and prevention of intermittent claudication have been reported in patients with peripheral vascular disease treated with carnitine. There are also data to suggest that carnitine may have potential in the treatment of congestive heart failure, the prevention of cardiac arrhythmias, and the cardiotoxicity associated with anthracycline therapy. Many additional studies are clearly needed, however, before the role of carnitine in the management of these conditions can be precisely defined.

One challenge for the future is to find safer and more effective pharmacologic therapies, and the data reviewed suggest that carnitine warrants further attention. Clearly, carnitine appears to be very safe and its use may be underutilized. Through careful study using rigid protocols, we should be able to determine the precise role for this agent in cardiovascular therapeutics.

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