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Review

Influence of L-carnitine and its derivatives on myocardial metabolism and function in ischemic heart disease and during cardiopulmonary bypass

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Abstract

Carnitine and its derivatives have recently been shown to protect cardiac metabolism and function in ischemic heart disease and other clinical conditions of myocardial ischemia. Potential mechanisms of this effect include an increase in glucose metabolism, a reduction of toxic effects of long-chain acyl-CoA and acyl-carnitine in myocytes, an increase in coronary blood flow and anti-arrhythmic effect. It has also been shown that propionyl-L-carnitine which penetrates faster than carnitine into myocytes is effective in inhibiting production of free radicals. Beneficial effects of carnitine supplementation have been demonstrated under a variety of clinical conditions such as acute cardiac ischemia, during extracorporeal circulation, in carnitine-dependent cardiomyopathy as well as in patients with chronic circulatory failure and in cardiogenic shock. However, further studies are required before carnitine administration could be recommended as a routine procedure in ischemic heart disease or before cardiopulmonary bypass. © 2001 Published by Elsevier Science B.V.

Keywords: Coronary disease; Energy metabolism; Heart failure; Ischemia; Myocytes; Ventricular function

1. Introduction

L-Carnitine (β-hydroxy-γ-trimethyl-amino-butyric acid) is a crucial component of activated fatty acids transport mechanism across the mitochondrial membrane [1]. Carnitine facilitates oxidation of long-chain fatty acids, modulates the ratio of CoA to CoA-SH, and is involved in trapping acyl residues from peroxisomes and mitochondria. Carnitine also participates in metabolism of branched chain amino acids and stabilizes cellular membranes. It is also a free radical scavenger and is likely to take part in control of nuclear transcription [1,2]. The primary sites for carnitine synthesis from 6-*N*-trimethylolysine are the liver and the kidneys, although the brain does have a small potential as well. Substrates that are indispensable for carnitine synthesis and are present in the diet are lysine and methionine, although the presence of vitamins C and B_6, and iron [3] is equally important. However, if the diet is deficient in carnitine, a considerable drop soon develops in its plasma concentration [4]. Minimum supplementation of carnitine in the diet to maintain its body stores constant ranges from 8 to 11 mg per day [4]. The richest source of carnitine is red meat, which contains about 5.5 μmol/g of tissue, and among plant-origin products — beans (0.72 μmol/g) and avocado.

The total content of carnitine in the human body is about 100 mmol (16 g) but it depends on the diet, muscle mass and the age [1]. Muscles contain 98% of that total amount, while 1.5 and 0.5% of carnitine are found in the liver and other tissues, respectively [5]. The total carnitine concentration in plasma is usually in the range of 42–85 μmol/l, and that of free carnitine in the range of 35–70 μmol/l [6]. Carnitine concentration in the heart is about 4.2 μmol/g of tissue, which is over three times higher, than that in the striated muscles (1.26 μmol/g), four times higher than that in the liver (0.94 μmol/g), and eight times

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higher than that in the kidney (0.52 μmol/g) [7]. The skeletal muscles and the heart lack potential for synthesizing carnitine.

Accumulation of carnitine in the heart is facilitated by active extraction of carnitine from plasma against a 60-fold concentration gradient [8]. Unlike in the liver, carnitine concentration in the myocardium and skeletal muscle is relatively independent of its temporary supply [9].

Over 95% of ingested carnitine is excreted in urine in humans [10]. The clearance of free carnitine is about four times lower than of acyl-carnitine (1.1 ml/min and 4.8 ml, respectively). There is evidence that a Na^+ dependent system exists driven by energy from the ATP hydrolysis. It is responsible for carnitine transport through the muscle cell membrane [11]. Carnitine transport to the mitochondria is carried out by a specific protein carrier [12]. Long-chain fatty acids constitute a basic substrate for oxidative energy metabolism in the myocardium. Following transport through the cellular membrane, they undergo activation to acyl-CoA in the cytoplasm or on the external mitochondrial membrane. Though some of activated fatty acids undergo esterification to triglycerides, majority becomes a substrate for β-oxidation in mitochondria. Carnitine has a basic role in transporting activated fatty acids from the cytoplasm into mitochondria, where β-oxidation occurs. Short- and medium-chain fatty acids are transported into the mitochondrial matrix without any carnitine assistance in the process. Long-chain fatty acid acyl groups are transported exclusively as carnitine esters by a carnitine carrier the translocase, which constitutes a transmembraneous protein in the inner mitochondrial membrane [13,14].

The 'carnitine system' consists mainly of carnitine, carnitine acyl-transferases, translocase, and transporting proteins located in plasma membranes. Carnitine palmitoyl transferase 1 (CPT 1) which is located on the internal side of the external mitochondrial membrane transfers activated long-chain acyl residues from acyl-CoA into carnitine. Carnitine translocase exchanges acyl-carnitine for carnitine from the matrix via the internal mitochondrial membrane. On the internal side of the inner mitochondrial membrane, carnitine palmitoyl transferase 2 (CPT 2) catalysis acyl-CoA synthesis from acyl-carnitine and matrix pool of CoA-SH (Fig. 1). Finally acyl-CoA undergoes mitochondrial β-oxidation with a release of energy in the ATP form. Carnitine lowers the ratio of intramitochondrial acyl-CoA to CoA and causes detoxification of accumulated acyl-CoA esters in patients with defective metabolism of glucose or acyl-oxidation. The above mechanism is impaired when mitochondrial β-oxidation disturbances develop in carnitine deficient patients [15].

Systemic carnitine deficiency manifests mainly as a dysfunction of skeletal muscles and myocardium, where fatty acids constitute a basic energy substrate. Other symptoms of carnitine deficiency also include hypoglycemia due to exhaustion of glucose reserves, which is an alternative substrate to fatty acids, hyperammonemia, hypoketonemia, coma, seizures, and developmental retardation, as well as the presence of lipid deposits in the histopathologic picture of the liver and muscles. Primary carnitine deficiencies result from inborn defects in specific proteins or in carnitine transferases. Secondary causes of L-carnitine deficiency include metabolic defects in fatty acid oxidation, mitochondrial myopathy, prematurity, L-carnitine deficiency in the diet, dialysis therapy, diabetes, and inadequate absorption from the gastrointestinal tract. Studies on carnitine concentration can indicate either an absolute deficit of carnitine when its level drops below 20 μmol/l, or its relative deficit when the ratio of carnitine esters to free carnitine is above 0.4 [11]. Absolute or

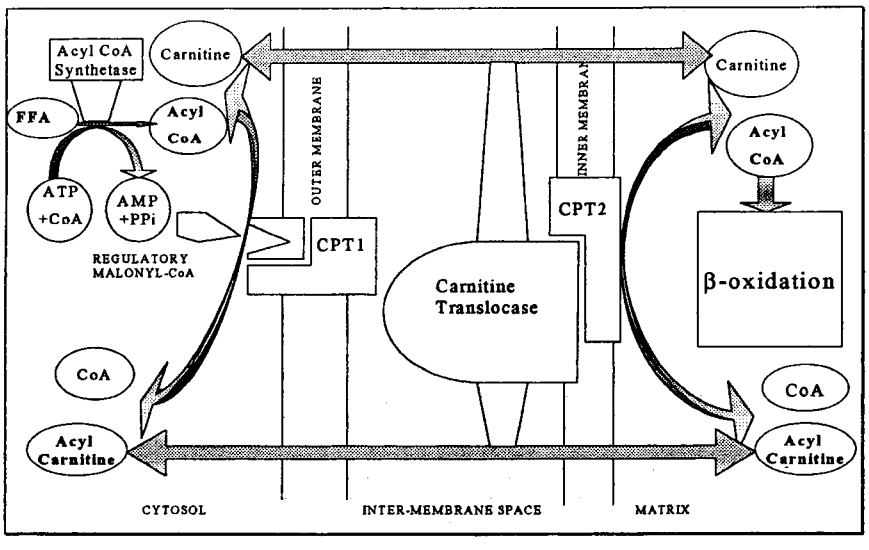

Fig. 1. Carnitine dependent transport of long-chain acyl groups through the mitochondrial membrane.

relative carnitine deficits develop in chronic congestive heart failure, acute myocardial ischemia, diseases of peripheral blood vessels, diabetes, and disturbances of lipid metabolism. The clinical importance of carnitine in the treatment of circulatory disorders was first demonstrated in 1973 when its deficit was discovered in patients with lipid cardiomyopathy and reduced fatty acid oxidation [16]. Additionally, carnitine administration has been proven clinically beneficial in other diseases characterized by carnitine deficit that include, among others, ischemic cardiomyopathy and peripheral atherosclerosis [2].

Positive clinical effects of carnitine administration were also observed in nervous system degenerative diseases, brain ischemia, chronic fatigue syndrome, Alzheimer's disease, and AIDS [17–19]. L-Carnitine in a long-term supplementation has been shown to be beneficial to the function of erythrocytes in hemodialysed patients [20]. Positive results of carnitine therapy are due to, among others, oxidation of fatty acids, the process which is linked with saving muscle glycogen reserves. A number of therapeutic effects possibly come from the interaction of carnitine and its derivatives with the elements of cellular membranes [21].

Some improvement in the muscle blood supply after carnitine supplementation has been related to vasodilatation. In diabetes, L-carnitine supplementation causes a decrease in triglyceride synthesis, a drop in the cellular free fatty acids uptake, and the removal from organism of excessive long-chain carnitine esters, as well as increase in glycolysis, oxidation of pyruvate, and improvement in neuronal transmission [22].

2. Disturbances of myocardial function and carnitine metabolism — experimental data

Carnitine is released from ischemic myocardium, and its concentration in the coronary sinus is proportional to the concentration of lactate [23,24]. These changes are reflected by a change in the ratio of free carnitine to carnitine esters in the heart. Anoxia caused by myocardial ischemia has been experimentally proven to be associated with the depletion of carnitine reserves and accumulation of toxic metabolites of fatty acid esterification, in consequence of restricted fatty-acids mitochondrial β-oxidation [25]. The result is a decrease of ATP concentration in the heart [26]. After only a few minutes of ischemia, free fatty acids, long-chain acyl-CoA esters and acyl-carnitine are all increased several times above the control level [27] and, after half an hour of ischemia, the free carnitine in the heart drops by half [26].

Long-chain acyl-carnitine esters are lipophylic and may readily damage membrane lipids and particularly, membrane bound enzymatic proteins [27]. This results in an increase of membrane fluidity and affects membrane ion transport. Inhibition of the sodium–potassium ATP-ase in sarcolemma results in a decrease of membrane rest-potential. In consequence, spontaneous action potentials may appear along with a delayed depolarization of action potential [28].

In the study of Silverman et al. carnitine supplementation had a positive and dose-dependent effect on preserving ventricle compliance and contractility of ischemic canine heart muscle, yet had no influence upon a decrease in ATP concentration induced by ischemia [25]. In another study, when oxygenated blood supply was restored, no recovery of lipid oxidation was observed unless carnitine deficiency had been compensated [29]. According to Liedtke et al. reduced carnitine reserves in the myocardium strengthen the negative influence of lipids and particularly of free fatty acids, on heart metabolism [29]. The positive carnitine influence seen in acute myocardial ischemia was explained by limiting a decrease in high-energy phosphates [30] and some improvement in glucose oxidation and lactate extraction [31]. Basic metabolic effects of carnitine supplementation during ischemia–reperfusion and its suggested clinical effects are presented in Fig. 2.

Following carnitine administration, some improvement in relaxation was observed in rat hearts with increased afterload [32]. However, when isolated rabbit hearts were studied, no improvement of contractility, heart rate, or coronary perfusion pressure was reported [32]. Broderick et al. demonstrated a more than two-fold increase in glucose metabolism after ischemia and reperfusion in rat heart preparations perfused with carnitine-enriched blood before the onset of ischemia [31].

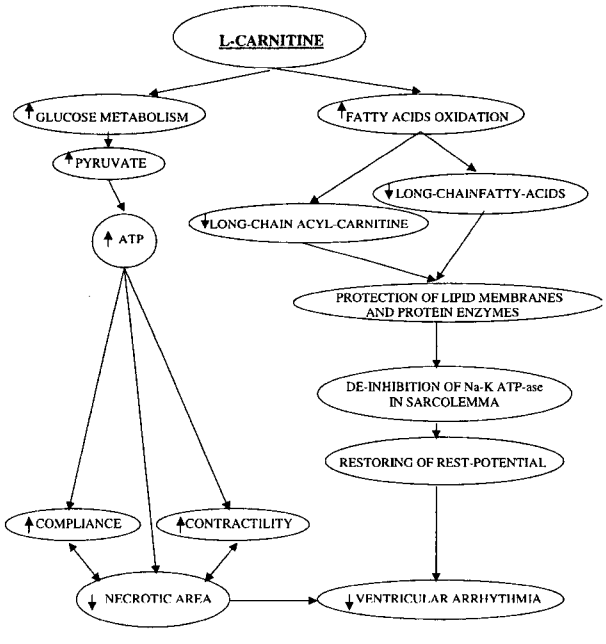

Fig. 2. Metabolic action of L-carnitine during myocardial ischemia–reperfusion, and its suggested clinical consequences.

A positive carnitine influence on myocardial metabolism during ischemia–reperfusion has been confirmed by increased ATP concentration in myocardium [33]. Another study demonstrated a beneficial effect of carnitine, added to cold cardioplegia, on the aorta flow velocity, the stores of ATP in myocardium, and the condition of mitochondria in rat hearts after reperfusion [34]. L-Carnitine supplementation beside causing an increase in ATP concentration, was associated with a lower amount of toxic esters [33], and with some improvement of systolic and diastolic function of diabetic rat hearts [35]. A similar therapy applied to a group of diabetes-free rats did not result in any change of heart function [35]. Experimental studies have demonstrated that in diabetic rats even a short-term carnitine supplementation caused an improvement of myocardial contractility after ischemia–reperfusion [36]. Administration of propionyl-L-carnitine to diabetic rats prior to ischemia and reperfusion resulted in a more complete recovery of post-reperfusion contractility [23].

In dogs without previous myocardial ischemia, supplementation of high carnitine doses was linked with a considerable increase (60–100%) in coronary blood flow [37]. In the same study a substantial increase in stroke volume and dP/dt for the left ventricle was reported.

When dogs with myocardial infarction were studied, a 50% lower ST elevation was observed in ECG, if L-carnitine was administered after the onset of ischemia [38]. Incubation of heart endothelium cells in a L-carnitine-rich environment causes a better recovery of their proper function during post-ischemic reoxygenation [39].

Protection of cell membranes and especially of membrane enzymes is a possible cause of electrophysiologic changes and antiarrythmic effect of carnitine. Studies on dogs treated with L-carnitine in doses of 40 and 80 mg/kg/min revealed a decrease in the heart rate by about 17 and 30%, respectively [31]. In canine heart preparations subjected to ischemia, a considerable carnitine-induced decrease in the frequency of ventricular arrhythmia, including ventricular fibrillation was observed [40]. The authors suggested it might have been caused by limiting the necrotic area rather than by direct antiarrythmic action. It has also been demonstrated that carnitine supplementation is connected to limiting heart rhythm disturbances that come from a high concentration of free fatty acids in dogs [41]. Carnitine administration to perfused isolated preparations of guinea pig hearts has substantially lowered the incidence of arrhythmia resulting from ischemia and reperfusion [42].

Propionyl-L-carnitine was demonstrated to be able to reduce the incidence of ventricle fibrillation during reoxygenation after ischemia in isolated preparations of guinea pig hearts [43].

Positive results of treatment with carnitine were observed in experimental heart failure. Both in guinea pigs and dogs subjected to the toxin of *Corynebacterium diphtheriae* an improvement was observed in the left ventricle function and in the time of survival in the groups treated with L-carnitine [44,45]. Application of propionyl-L-carnitine to volume-loaded rat hearts was associated with an improvement in ventricle function without a simultaneous increase in oxygen consumption [46]. Schonekess et al. have reported an improvement in the function of hypertrophied myocardium and an increase in carbohydrate oxidation in rats treated with propionyl-L-carnitine [47]. Another study reported a decrease in mortality in hamsters with cardiomyopathy treated with carnitine [48]. There have also been contradictory reports, which presented a positive influence of inhibiting endogenic carnitine synthesis upon ischemic rat hearts [49]. In summary, relative myocardial carnitine deficiency is observed during ischemia and many experimental data suggest that some negative metabolic and biologic effects of ischemia, as well as heart failure are alleviated by carnitine supplementation.

3. Biological effects of carnitine and propionyl-carnitine administration

It has been suggested to treat metabolic dysfunction resulting from carnitine deficiency not only by administering L-carnitine, but also its derivative — propionyl-L-carnitine (Table 1). Some biologic properties of propionyl-L-carnitine suggest that beneficial clinical effects could be enhanced when compared to L-carnitine. Propionyl-L-carnitine has higher affinity for the plasma membrane transport system. It is more lipophylic and penetrates myocytes faster than L-carnitine [50]. Moreover, the propionyl residue of propionyl-L-carnitine can be metabolized to the succinate, a substrate of citric acid cycle [51]. Propionyl-L-carnitine has also protective properties for blood vessels and the energy reserves of ischemic striated muscles [52]. L-Carnitine and propionyl-L-carnitine were shown to protect the ischemic myocardium against oxidative stress, which is one of the basic mechanisms leading to a post-ischemic myocardial dysfunction known as 'stunning' [53]. Ferrari et al. have published interesting study concerning the maintenance of oxidative phosphorylation and prevention of calcium ion influx into mitochondria during reperfusion of rabbit hearts treated with propionyl-L-carnitine before the onset of ischemia [54]. Protection of the heart against oxidative stress during reperfusion was demonstrated after pre-ischemic administration of carnitine and its derivatives, particularly propionyl-L-carnitine [2]. Propionyl-L-carnitine does have a potential for inhibiting production of free hydroxyl radicals. Endothelial cellular membranes are better protected by propionyl-L-carnitine against Fe^{2+} and Fe^{3+} ions induced peroxide production, the protection being possibly due to ion chelating [39].

The protective effect of propionyl-L-carnitine in perfused rat hearts is dose-dependent and also depends on the time of administration, provided it is administered before

Table 1
Metabolic, experimental and clinical effects of carnitine and propionyl-L-carnitine supplementation on cardiovascular system

	Metabolic	Experimental	Clinical
L-Carnitine	Increased ATP concentration, decrease of long-chain fatty-acids esters in myocardium [33,66]	Positive and dose-dependent effect on preserving ventricle compliance and contractility of ischemic canine heart muscle [25]	Decreased mortality and the rate of circulatory failure in acute myocardial infarction [57]
	When added to cardioplegic solution, improved mitochondrial function in rat myocardium was observed after reperfusion [34]	Improvement of systolic and diastolic function in diabetic rat hearts [35]	Decreased diameter of the left ventricle in congestive heart failure [79]
	Substantial increase in glucose metabolism in rat hearts after ischemia and reperfusion [31]	In high doses — a considerable increase in coronary blood flow in dogs [37]	Increase in claudication distance [84]
	Necessary factor for recovery of lipid metabolism and oxidation of accumulated fatty-acids during reperfusion after ischemia [29]		
Propionyl-L-carnitine[a]	Protection of endothelium against free-radicals [39]	Better recovery of contractility after reperfusion when administered to diabetic rats prior to ischemia [23]	Increase in stroke volume in patients with myocardial ischemia [59]
			Increase in ejection fraction in congestive heart failure [76]
	Stabilization of plasmatic membranes [39]	Improvement of ventricular function of volume-loaded rat hearts [46]	
	Anaplerotic function-providing substrates for citrate acid cycle [51]		Lower incidence of arrhythmia in hemodialysed patients [63]
		Improvement of hypertrophied rat myocardial function [47]	
		Decreased incidence of ischemia-related arrhythmia and ventricle fibrillation in guinea pigs hearts [42]	Lower incidence of ventricular arrhythmia in acute myocardial infarction [64]

[a] Being an L-carnitine derivative, propionyl-L-carnitine also possesses all metabolic properties of L-carnitine.

post-ischemic reperfusion begins [55]. As suggested in the study, propionyl-L-carnitine may also have a role in stabilizing plasma membranes and in lowering the purine release from the perfused rat heart [39].

From the accumulated results it seems that positive biological effects observed after propionyl-L-carnitine are more evident that after L-carnitine administration. Better penetration into myocytes and supplying a substrate for the citric acid cycle can explain this observation in short-term supplementation. Inhibiting free-radicals generation and stabilizing plasma membranes may be other contributing factors.

4. Carnitine and circulatory diseases — clinical studies

4.1. Ischemic heart disease

A decreased carnitine concentration in the heart was observed in patients who died of myocardial infarction [56]. In patients with acute myocardial infarction, a four-fold increase was observed in free carnitine elimination and almost a two-fold increase in the elimination of short-chain carnitine esters by kidney [20]. Arsenian et al. demonstrated a decrease in mortality and incidence of circulatory failure in a group of patients with acute myocardial infarction, who were administered 3 g of carnitine along with solution of glucose, insulin, potassium and magnesium [57]. Propionyl-L-carnitine used in doses of 15 mg/kg caused a slight decrease in peripheral vascular resistance in patients with stable coronary disease, but due to a simultaneous increase in stroke volume, no decrease in arterial blood pressure was observed [58].

A similar dose administered to patients with ischemic heart disease caused in a short time (5 min) a 43% increase in lactate uptake by myocardium and increase in stroke volume by 8% [59]. On the other hand, administration of L-carnitine in a single dose of 40 mg/kg to patients with stable coronary heart disease did not cause any change in the heart rate at rest or in systolic and diastolic arterial pressure [60].

Coronary artery sclerosis is particularly common in diabetic patients. Disturbances of myocardial contractility in diabetic patients are generally associated with a higher incidence of coronary heart disease in this population. Many diabetics, however, suffer from decreased myocardial contractility in spite of negative coronarographic examinations. The causes of impaired heart contractility in diabetic patients who present no changes detectable by coronarography include, among others, microangiopathy and metabolic disturbances. Carnitine deficiency is now the best recognized condition of the latter. Decreased level of free and total carnitine in diabetes, with a simultaneous increase in concentrations of long-chained acyl-CoA and long-chain carnitine esters has been shown [23].

Some correlation has been also demonstrated between the left ventricular contraction index and long-chain acyl-

carnitine concentration in the myocardium during reperfusion in patients after mitral valve replacement [61]. These data suggest, in line with the results of experimental studies that carnitine and its derivatives protect human ischemic heart against oxidative stress not only by modifying carnitine acyl-transferase activity and metabolic effect, but by other mechanisms as well [21].

4.2. Arrhythmia

Heart electrophysiology after carnitine administration (30 mg per kg body weight over 3 min) did not show any changes either in the conductivity time or in refraction period. The cycle duration in the sinus node was shortened by 5%, while the arterial blood pressure remained unchanged [62]. It has been shown that the incidence of ventricular and supraventricular arrhythmia could be limited during hemodialysis in chronic renal failure [63]. A prolonged L-carnitine therapy in angina pectoris was associated with a considerable decrease in the frequency of ventricular arrhythmias [64]. Rizzon et al. noticed a statistically significant decrease of the frequency of ventricular arrhythmia in a group of patients with acute myocardial infarction who were administered 100 mg of carnitine per kg of body weight [65]. Although the studied groups of patients were small, L-carnitine administration to patients with ischemic heart disease appears to be a promising therapy of ischemia-induced arrhythmia as potentially addressed to restoring of membrane rest-potential.

4.3. Cardiopulmonary bypass surgery

Oral administration of carnitine (1 g) for 2 days before the coronary artery bypass graft (CABG) operation was associated with a higher ATP concentration and a more favourable ratio of free carnitine to long-chain acyl-carnitine in the atrial muscle [66]. Administration of high L-carnitine doses for 3 days prior to the extracorporeal circulation was not linked to an improvement of hemodynamic parameters, although a biopsy of septum revealed a better preserved cellular ultrastructure [67]. On the other hand, in patients with a low ejection fraction a dose of 360 mg of L-carnitine added to cardioplegia was demonstrated to have a positive influence on the stroke volume immediately after weaning from extracorporeal circulation [68]. In patients after CABG, L-carnitine supplementation has been shown to be associated with an increased uptake of free fatty acids by myocardium and with their lower concentration in blood [2].

4.4. Circulatory failure

Early reports on carnitine in the treatment of circulatory failure were concerned with its application in cases of carnitine deficiency syndrome. Carnitine deficiency syndromes can be divided into systemic and myopathic in nature. The former is characterized by a low carnitine concentration both in muscles and the blood, and the latter is known for a low carnitine concentration in muscles coexisting with the proper carnitine concentration in blood. This division enables assessment of the rationale for using carnitine in the treatment of concurrent circulatory failure. Cardiomyopathies that coexist with a low blood carnitine level are generally well treatable with carnitine [69,70]. Myopathies and cardiomyopathies with proper blood carnitine concentration prevalently do have some acyl-CoA dehydrogenase deficiency or functional disturbances of carnitine transport proteins [71]. However, increased carnitine concentrations in blood have been also seen in cardiomyopathic patients [72]. In dilated cardiomyopathy patients who underwent heart transplantation for circulatory failure, a low carnitine concentration was found both in the blood and myocardium [73]. Myocardial carnitine concentration was also lower in rheumatic heart disease [74]. Administration of carnitine to children with diphtheria was found to have reduced substantially the incidence of myocarditis [75]. One-month propionyl-L-carnitine therapy in doses of 1.5 g for 24 h in patients with congestive heart failure resulted in an increased ejection fraction [76]. Hemodialysed patients were observed to have a lower free-carnitine concentration in blood, despite normal concentration of total carnitine. After a 12-month carnitine therapy at 500 mg/24 h dose the same patients had improved circulatory function in electrocardiographic examination [77].

Pugliese et al. observed a decrease in pulmonary arterial pressure, in the heart rate in patients with hepatic cirrhosis after administration of 30 mg of L-carnitine per kilogram body weight [78]. Both short- and long-term propionyl-L-carnitine supplementations, in patients with congestive heart failure resulted in decreased pressure in the pulmonary artery and the left ventricle diameter [79]. One study on patients with shock who were given high L-carnitine doses did demonstrate clinical improvement [80], while another report concluded that a 12-h acetyl-carnitine administration to patients in shock was associated only with a slight improvement in selected hemodynamic parameters [81].

In the light of these collected results, application of carnitine appears promising in circulatory failure. However, except for carnitine deficiency syndromes, this has not been satisfactorily proven.

4.5. Peripheral blood vessel diseases

The data on the influence of carnitine and its derivatives in cases of peripheral blood vessel disease generally come from experimental studies. Accordingly, propionyl-carnitine has a potential for inhibiting thrombosis induced in the rat's tail [82]. Corsico et al. observed the protective properties of propionyl-L-carnitine for the condition and

function of muscles as well as the condition of vessels that were damaged with sodium lauryl-sulphate [53]. Patients with peripheral blood vessel disease were found to have on exertion an increased blood concentration of total carnitine as well as long- and short-chain acyl-carnitine [83]. Following a 3-week carnitine therapy, these patients had a longer claudication distance [84]. Beneficial effects of propionyl-L-carnitine in peripheral blood vessel disease can be not only related to an improved metabolism of ischemic muscles. They are also possibly linked to some potential for limiting a negative influence of endothelin on blood vessels [85] or to increasing tissue concentration of plasminogen activator, or to an improvement in the rheological properties of erythrocytes [86]. Studies have also proven that propionyl-L-carnitine has a vasodilative action independent of nitric oxide, but mediated by prostaglandins [87].

An increasing amount of data supports the thesis of the beneficial effects of carnitine in patients with ischemic heart disease and ischemia-related arrhythmia, circulatory failure and peripheral vascular disease. The results of studies on hemodynamic effects of carnitine and its derivatives administration could possibly be more univocal, if the studied groups were more homogenic concerning poor ventricular function and coexisting state of carnitine deficiency.

5. Side effects

Carnitine preparations administered orally can occasionally cause heart-burn and dyspepsia. Two patients treated with intravenous carnitine in doses of 6 g complained of blurred vision and one reported a headache [88]. Fairly high doses of carnitine administered orally may produce an unpleasant body odor that is similar to that of rotten fish. There are no reports to date of serious side effects caused by L-carnitine and its derivatives, and most clinical studies have claimed there were not any undesired effects.

6. Conclusions

The results reviewed in this article indicate that carnitine and propionyl-L-carnitine exert a positive metabolic and functional effect on myocardium in ischemic heart disease and in heart failure. The accumulated data resulting from experimental and clinical studies and general knowledge of myocardial metabolism in ischemia and reperfusion, allows us to expect encouraging clinical results especially in carnitine-deficient patients. However, some conflicting results do not permit definitive conclusion to be drawn about the efficacy of the action of carnitine and its derivatives on ischemic and reperfused myocardium. Additional studies performed under well-controlled conditions are needed to further elucidate the rationale for carnitine administration in ischemic heart disease and before cardiopulmonary bypass surgery.

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