Therapeutic Effects of L-Carnitine and Propionyl-L-carnitine on Cardiovascular Diseases: A Review

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ABSTRACT: Several experimental studies have shown that levocarnitine reduces myocardial injury after ischemia and reperfusion by counteracting the toxic effect of high levels of free fatty acids, which occur in ischemia, and by improving carbohydrate metabolism. In addition to increasing the rate of fatty acid transport into mitochondria, levocarnitine reduces the intramitochondrial ratio of acetyl-CoA to free CoA, thus stimulating the activity of pyruvate dehydrogenase and increasing the oxidation of pyruvate. Supplementation of the myocardium with levocarnitine results in an increased tissue carnitine content, a prevention of the loss of high-energy phosphate stores, ischemic injury, and improved heart recovery on reperfusion. Clinically, levocarnitine has been shown to have anti-ischemic properties. In small short-term studies, levocarnitine acts as an antianginal agent that reduces ST segment depression and left ventricular end-diastolic pressure. These short-term studies also show that levocarnitine releases the lactate of coronary artery disease patients subjected to either exercise testing or atrial pacing. These cardioprotective effects have been confirmed during aortocoronary bypass grafting and acute myocardial infarction. In a randomized multicenter trial performed on 472 patients, levocarnitine treatment (9 g/day by intravenous infusion for 5 initial days and 6 g/day orally for the next 12 months), when initiated early after acute myocardial infarction, attenuated left ventricular dilatation and prevented ventricular remodeling. In treated patients, there was a trend towards a reduction in the combined incidence of death and CHF after discharge. Levocarnitine could improve ischemia and reperfusion by (1) preventing the accumulation of long-chain acyl-CoA, which facilitates the production of free radicals by damaged mitochondria; (2) improving repair mechanisms for oxidative-induced damage to membrane phospholipids; (3) inhibiting malignancy arrhythmias because of accumulation within the myocardium of long-chain acyl-CoA; and (4) reducing the ischemia-induced apoptosis and the consequent remodeling of the left ventricle. Propionyl-L-carnitine is a carnitine derivative that has a high affinity for muscular carnitine transferase, and it increases cellular carnitine content, thereby allowing free fatty acid transport into the mitochondria. Moreover, propionyl-L-carnitine stimulates a better efficiency of the Krebs cycle during hypoxia by providing it with a very easily usable substrate, propionate, which is rapidly transformed into succinate without energy consumption (anaplerotic path-

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way). Alone, propionate cannot be administered to patients in view of its toxicity. The results of phase-2 studies in chronic heart failure patients showed that long-term oral treatment with propionyl-L-carnitine improves maximum exercise duration and maximum oxygen consumption over placebo and indicated a specific propionyl-L-carnitine effect on peripheral muscle metabolism. A multicenter trial on 537 patients showed that propionyl-L-carnitine improves exercise capacity in patients with heart failure, but preserved cardiac function.

KEYWORDS: myocardial metabolism; myocardial ischemia; levocarnitine; propionyl-L-carnitine

LEVOCARNITINE

Levocarnitine occurs naturally as an essential cofactor of fatty acid metabolism, which is synthesized endogenously or obtained from dietary sources. It is a cofactor of several enzymes (carnitine translocase, acylcarnitine transferases I and II). Its main role is to shuttle long-chain fatty acids and activated acetate across the inner mitochondrial membrane.[1] A specific translocase facilitates this exchange of long-chain acylcarnitine and acetylcarnitine. Levocarnitine acts as the shuttle for the end products of peroxisomal fatty acid oxidation and for the α-ketoacids derived from the branched-chain amino acids. The α-ketoacids are transferred into the mitochondrial matrix for completing oxidation. Furthermore, levocarnitine modulates the intramitochondrial acyl-CoA/CoA ratio. The reaction is freely reversible and is catalyzed by the mitochondrial enzyme, carnitine acetyltransferase. In the case of inadequate carnitine concentrations, the reaction would be pushed in the direction of acyl-CoA moiety, resulting in decreased free CoA concentrations within the mitochondrial matrix. This shift, in turn, interferes with all reactions that are dependent upon the availability of free CoA and downregulates intermediary metabolism within the mitochondrion.

Although the major role of levocarnitine is in free fatty acid metabolism, it also enhances carbohydrate utilization.[2] Several results obtained in intact animals support this view. Treatment with levocarnitine resulted in a significant improvement in several parameters of mechanical function of the heart during a period of mild ischemia.[3] These data were concomitant with a lower accumulation of acyl-CoA. No major changes of myocardial mechanical functions and systemic pressure were noted during the infusion of levocarnitine in the preischemic period. In addition, in these studies, the authors also investigated the effects of D-carnitine and DL-carnitine.[4] It is interesting to note that the D-isomer was biologically inert. In contrast, the results obtained in the DL-isomer-treated group were between L-isomer and control group results. These observations clearly demonstrate an isomer-specific effect, although the biochemical bases remain unknown.

Levocarnitine does not have hemodynamic effects in healthy volunteers or patients with CAD. However, an improvement of individual maximal aerobic power (VO_{2max}) is demonstrated in healthy subjects[5] and athletes[6] after chronic treatment with levocarnitine (4 g daily over a period of 2 weeks). Thus, levocarnitine has to affect heart metabolism. Its effects on myocardial metabolism at rest or during pacing-induced tachycardia have been studied in coronary-artery-diseased patients with normal left ventricular function.[7–9] At rest, levocarnitine (40 mg/kg administered intravenously as a single bolus over 5 to 45 min before the second pacing)

caused (a) a significant reduction in arterial concentration of free fatty acids owing to increased myocardial uptake; (b) a reduction in myocardial uptake of glucose; (c) no major changes in myocardial uptake of lactate; and (d) no significant increase in the overall oxygen consumption of the heart. During sinus pacing, levocarnitine caused (a) a decrease of myocardial lactate production, maintaining a positive extraction relative to that seen in the untreated or placebo-treated group; and (b) an increase in myocardial free fatty acid extraction.

There are widespread systemic metabolic effects of levocarnitine, including increased glucose utilization in patients with insulin-dependent diabetes[2] and reduction of blood lactate concentration.

There is a close relationship between tissue carnitine levels and liver glycogen content. Oral levocarnitine (3–4 g daily) normalizes plasma total cholesterol or triglyceride levels (or both) and increases high-density lipoprotein (HDL)–cholesterol in patients with type II and type IV hyperlipoproteinemia over a 2-month period.[10,11]

Placebo-controlled studies performed in patients with stable chronic effort angina suggest that levocarnitine given acutely (40 mg/kg iv) or chronically (1–3 g daily for a month) improves exercise capacity and the electrocardiographic manifestations of ischemia.[12–14]

Oral levocarnitine (4 g daily for 21 days) improves the maximal walking distance of patients with intermittent claudication caused by peripheral arterial disease.[15]

THERAPEUTIC USE OF LEVOCARNITINE

Interestingly and importantly, there is not any known disease or syndrome in which levocarnitine administration is contraindicated. Thus, levocarnitine is extremely safe.

There are several therapeutic uses of L-carnitine:

(1) Treatment of primary carnitine deficiency syndromes:

(i) systemic carnitine deficiency;
(ii) myopathic carnitine deficiency.

(2) Treatment of secondary carnitine deficiency/insufficiency states:

(i) genetically determined metabolic errors (mainly organic acidurias);
(ii) chronic intermittent hemodialysis in end-stage renal failure;
(iii) valproate-induced hepatotoxicity;
(iv) cardiac and/or skeletal muscle ischemia.

In this report, we concentrate only on secondary carnitine deficiency since primary has already been discussed elsewhere in this volume.

TREATMENT OF SECONDARY CARNITINE DEFICIENCY

Genetically Determined Metabolic Errors

The genetically determined conditions are recessive. No significant prevalence of these disorders is found between sexes or in different ethnic groups. The symptoms

appear in children from 0 to 13 years of age and affect fatty acid metabolism. The most common findings are weakness, coma, failure to thrive, hypoglycemia, metabolic acidosis, low serum carnitine (<20 μM), elevated esterified/free carnitine ratio (>0.40), and dicarboxylic aciduria.[1,16] Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency has emerged as the most distinctive organic aciduria associated with carnitine deficiency.[17] Some of the earliest examples of "primary systemic carnitine deficiency" have proved to be secondary to MCAD deficiency.[18–20] The metabolic errors are diverse. The specific defects identified are short-chain acyl-CoA dehydrogenase (SCAD) deficiency, MCAD deficiency, long-chain acyl-CoA dehydrogenase (LCAD) deficiency, multiple acyl-CoA dehydrogenase (MAD) deficiency, isovaleric acidemia, propionic acidemia, methylmalonic aciduria, hydroxymethylglutaryl-CoA lyase deficiency, glutaric aciduria type I, β-kethiolase deficiency, homocystinuria, 5-methylene tetrahydrofolate reductase efficiency, adenosine deaminase deficiency, ornithine transcarbamoylase heterozygote state, cystinosis, and cytochrome oxidase deficiency. These diverse conditions are associated with impaired esterification of carnitine and decreased serum or tissue carnitine concentrations.[18]

Administration of exogenous levocarnitine has positive metabolic effects, buffering the excess of acyl-CoAs in the mitochondria, and thus yielding formation of acylcarnitines. These are shuttled out of mitochondria and eliminated in the urine.[19] Improvement of the general conditions and muscle tone, and reduction of recurrent metabolic attacks, reflects the detoxification role of carnitine conjugation. The responder population is approximately 50% of the total.[20–22]

Carnitine Deficiency in Patients with End-Stage Renal Failure Undergoing Long-Term Intermittent Hemodialysis

Serum carnitine concentration was found to decline by ~75% during one hemodialysis session.[23] In patients undergoing hemodialysis, free carnitine concentration is subnormal and acylcarnitine is elevated, the latter probably being a result of abnormal fatty acid oxidation combined with diminished renal excretion. Often, the muscle concentration is also subnormal.[24] A variety of metabolic disorders and symptoms associated with the long-term intermittent hemodialysis are treated with levocarnitine. The doses range from 100 mg/kg when administered intravenously after each dialysis session, and from 1–2 g daily when administered orally. This treatment might reduce the increased concentration of triglycerides, which occurs in patients under dialysis,[25,26] but not univocally so.[27,28] Crossover, double-blind controlled trials demonstrated that levocarnitine treatment induces a reduction in the incidence of intradialytic hypotension and muscle cramps[24–29] and attenuates cardiac arrhythmias.[30] Similar observations have been reported using the oral or the intravenous administration. In addition, patients under dialysis receiving oral levocarnitine normally experience significant increases in hematocrit.[25,31,32]

Valproate-Induced Hepatotoxicity

Valproate has been in worldwide clinical use for the treatment of epilepsy. However, its chronic administration can cause hepatotoxicity and carnitine deficiency.[33,34] Treatment with carnitine was proposed to reduce valproate toxicity.

Studies demonstrated that oral levocarnitine administration (1–2 g daily) significantly restores the serum concentration of total carnitine and decreases the incidence of liver dysfunction.[35–37]

Cardiac and/or Skeletal Muscle Ischemia

The finding in experimental animals and in humans[38,39] that the ischemic and the failing myocardium has low content of free carnitine supports the concept that myocardial ischemia is often accompanied by relative carnitine insufficiency. Administration of carnitine (20–140 mg/kg iv) to CAD patients subjected to atrial pacing increases significantly pacing duration, maximal heart rate, and rate-pressure product. Concomitantly, it reduced left ventricular end-diastolic pressure and lactate production, which is converted into a net extraction.[7–9,40] A few placebo-controlled studies suggest that both the acute (40 mg/kg iv) and the prolonged oral administrations of levocarnitine (1–3 g daily) improve exercise capacity and the electrocardiographic manifestations of ischemia.[12–14] In no study was treatment with levocarnitine compared with standard antianginal therapy.

Tissue fatty acid accumulation during myocardial ischemia is a cause of ventricular arrhythmias. Because of this notion, a double-blind, parallel, placebo-controlled study was carried out in 56 patients suffering from acute myocardial infarction. After a clinical stratification, patients were randomly allocated to receive placebo or levocarnitine at a dose of 100 mg/kg every 12 h for 36 h. The end point of the study was the reduction in number of premature ventricular beats evaluated by Holter recording over a period of 48 h. Active treatment significantly decreased the ectopic ventricular beats, probably because of metabolic effects that avoid fatty acid myocardial accumulation. This hypothesis is suggested by the high concentration of long- and short-chain carnitine esters found in the urine of the treated patients at 48 h after drug infusion.[41]

All these data have prompted the conduction of a multicenter trial on 472 patients to evaluate the effects of levocarnitine administration on left ventricular remodeling after acute anterior infarction, called the Levocarnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial.[42] This randomized, double-blind, placebo-controlled, multicenter study was performed to evaluate the effects of levocarnitine administration on long-term left ventricular dilatation in patients with acute myocardial infarction. Placebo or levocarnitine (9 g iv daily for the first 5 days and then 6 g orally daily) was administered for 12 months. The primary end points of the trial were left ventricular volumes and ejection fraction, at 12 months after the emergent event, assessed by two-dimensional echocardiography.

Treatment with the active compound resulted in a significant reduction of left ventricular dilatation. The percentages of both end-diastolic and end-systolic volumes were reduced significantly in the levocarnitine-treated group. No modification of left ejection fraction was observed. The incidences of death, congestive heart failure, and/or ischemic events were less in the carnitine-treated groups.

These encouraging data on survival have prompted another multicenter trial on over 2000 patients aimed to evaluate the short-term effects (6 months) of early levocarnitine administration on clinical end points (the CEDIM II trial) in patients with acute myocardial infarction. The study has been completed and the results will be available soon.

The effects of levocarnitine on peripheral muscle have also been studied.[43] The first double-blind, crossover study was designed to evaluate the effects of levocarnitine in 20 patients randomly assigned to receive placebo or levocarnitine (2 g twice daily, orally) for a period of 3 weeks. The end point was the difference of absolute walking distance at the end of each treatment, which was significantly increased by active treatment.

These data were concomitant with a reduction of popliteal venous lactate concentration and no important modification of blood flow. Biopsy of the ischemic muscle, performed before and after levocarnitine treatment, showed an increase of total carnitine level. The authors concluded that levocarnitine treatment improves the exercise duration of patients with peripheral vascular disease, probably through a metabolic mechanism.[43] To further prove this hypothesis, another study was carried out in which blood flow was measured in the affected limb by impedance plethysmography under resting conditions at 2-min intervals for 10 min after a 5-min period of ischemia in the same limb. After a washout period of 2 weeks, patients were randomly assigned to receive placebo or levocarnitine, 3 g iv as a bolus, followed by continuous intravenous infusion of 2 mg/kg/min for 30 min. At the end of perfusion, ischemia was induced by abolishing the blood flow.

Levocarnitine treatment did not modify blood flow under resting conditions; however, it significantly increased postischemic blood flow, suggesting an improvement in functional circulatory reserve in patients with peripheral vascular disease.

PROPIONYL-L-CARNITINE (PLC)

PLC is formed via carnitine acetyltransferase from propionyl-CoA, a product of methionine, threonine, valine, and isoleucine, as well as of odd-chain fatty acids. Pharmacokinetic studies demonstrated that, in humans, plasma concentration of PLC increases following intravenous administration and then decreases to baseline values within 6 to 24 h.[44] This life span varies with dosage. PLC increases plasma and cellular carnitine content, thus enhancing free fatty acid (FFA) oxidation in carnitine-deficient states, as well as increasing glucose oxidation rates.[45]

PLC is highly specific for skeletal and cardiac muscle;[46] it carries the propionyl group and enhances the uptake of this agent by myocardial cells.[47] This is particularly important because propionate can be used by mitochondria as an anaplerotic substrate, thus providing energy in the absence of oxygen consumption.[48] Note that propionate alone cannot be administered because of its toxicity.[49] Finally, because of the particular structure of the molecule with a long lateral tail, PLC has a specific pharmacologic action that is independent of its effect on muscle metabolism; this results in peripheral dilatation and positive inotropic effects.[50,51]

Because of PLC's characteristics, it was hypothesized that it could provide adjuvant benefit over standard therapy by specifically improving impaired metabolism of skeletal and heart muscle in patients with CHF. When administered acutely to an isolated and perfused heart preparation, PLC does not modify left ventricular pressure.[52] When administered intravenously through *in vivo* preparation, PLC causes a dose-dependent, short-lasting enhancement of cardiac output in dogs studied under open and closed chest conditions.[44,45] These responses are not modified by α- or β-adrenergic blockade or by administration of calcium antagonists. In

addition, PLC causes coronary vasodilatation with reduced oxygen extraction; these effects are not seen with levocarnitine alone. Thus, all of the cardiovascular actions of PLC can be attributed to its pharmacologic properties rather than to its role as a metabolic intermediate.

PLC hemodynamic effect was evaluated in 10 patients with coronary artery disease with normal LV function.[46,47] The drug was intravenously administered at 15 mg/kg. PLC improved the stroke volume and reduced the ejection impedance as a result of decreased systemic and pulmonary resistances and increased arterial compliance. Total external heart power improved with a proportionally smaller increase in the energy requirement; this suggested that PLC has a positive inotropic property.

PLC increased the performance of the aerobic myocardium independently from changes of peripheral hemodynamics or coronary flow when administered chronically to the animals several days before the isolation of the heart.[48–52] To investigate whether the chronic effect is specific for PLC or is due to levocarnitine or propionic acid, we designed experiments in which rabbits were treated for 10 days with saline, levocarnitine, propionic acid, or PLC (all at 1 mmol/kg). Propionic acid resulted in 98% mortality after 10 days. No deaths occurred after PLC or levocarnitine treatment. Treatment with levocarnitine failed to modify the volume-pressure curves of the isolated heart. Conversely, treatment with PLC prevented the decrease of the optimum developed pressure and the rise in end-diastolic pressure, which remained constant even after overstretching. It has been postulated that the rise in end-diastolic pressure enhanced the mechanical performance of the heart by improving its metabolism.[53] It is known that pyruvate increases heart contractility, which allows a more efficient energy use.[49] Administration of pyruvate leads to a higher cytosolic phosphorylation potential, which in conjunction with a reduced inorganic phosphate (Pi) concentration translates into an increased contraction. We investigated whether a similar mechanism is the basis for the PLC effects. Energy metabolism does not seem to be involved because high-energy phosphates, Pi, and mitochondrial function remain unchanged after chronic PLC administration. These findings, however, led to some important implications. Usually, typical inotropic agents, such as digitalis, calcium, and adrenergic compounds, stimulate contractility by increasing myofibrillar energy use at the expense of energy supply. Consequently, these agents cause a decline in the phosphocreatinine (PCr)/Pi ratio; this suggested that they place the heart in a supply/demand imbalance.[49] This was not the case for PLC.

Energy metabolism remained unchanged despite the increase in myocardial performance. During the repolarization phase, which is modified by PLC, important events occurred that influenced contractility.[54] It is appealing to correlate the effect on papillary muscle action potential duration with that on cardiac mechanical performance because PLC, but not levocarnitine, affects both of them.

Broderick *et al.*[55] conducted research with ischemic myocardium on isolated rat hearts and global no-flow ischemia that showed that, during the reperfusion of previously ischemic hearts, PLC stimulated glucose oxidation and significantly improved the functional recovery as measured by heart rate and peak systolic pressure. This supported the theory that carnitine's beneficial effects on ischemic myocardium are the result of its ability to overcome the inhibition of glucose oxidation that is induced by increased levels of fatty acids. Another study suggested an intracellular mechanism of action and implied that better protection is provided if the agent is administered before ischemic insult.[56]

Paulson *et al*.[57] studied isolated rat hearts that were subjected to global low-flow ischemia. During reperfusion, the group that was treated with PLC exhibited significantly greater recovery of all hemodynamic variables. In a similar preparation, 1 mmol PLC had no protective effect, whereas 5.5 and 11 mmol improved the recovery of cardiac output. The beneficial effect is greater than that of L-acetylcarnitine or levocarnitine on a molar basis. PLC was also found to directly improve postischemic stunning.[57] Specific experimental studies were conducted on the efficacy of this agent with respect to CHF.[57,58] In particular, treatment with PLC (50 mg/kg, intra-arterially) for 4 days significantly improved the hemodynamics of pressure overloaded (by constriction of the abdominal aorta) in conscious rats.[58] In another study, papillary muscles were isolated from rats that had been treated with 180 mg/kg PLC for 8 weeks, starting from weaning.[59] Aortic constriction was performed at 8 weeks of age and lasted for 4 weeks. The papillary muscles of untreated animals showed increased time-to-peak tension and a reduced peak rate of tension rise and delay. PLC normalized all of these parameters.[59]

In an infarct model of CHF, chronic administration of PLC (60 mg/kg orally given for 5 months) positively influenced ventricular remodeling; it was equally as effective as the ACE inhibitor, enalapril (l mg/kg orally), in limiting the magnitude of LV dilatation estimated by pressure-volume curves. PLC limited the alterations in ventricular chamber stiffness that were induced by infarction at low and high filling pressures.[60] In isolated myocytes obtained from infarcted rats, PLC increased peak systolic calcium, peak shortening, and velocity of cell shortening to a greater extent than in normal cells.[61] Pasini *et al*.[62] investigated the effects of PLC (250 mg/kg by intraperitoneal injection for 2 months) on the isolated and perfused heart from rabbits with streptozotocin-induced diabetes.[62] Cardiac performance was determined under basal conditions and during a stepwise increase in volume of a saline-filled balloon that was inserted into the LV. PLC prevented the decrease in developed pressure and the increase in diastolic pressure because of the progressive filling of the LV balloon. The same treatment also prevented the depression in the function of the sarcoplasmic reticulum that was observed in untreated rats. Calcium-stimulated ATPase activity, calcium uptake, and magnesium ATPase activity were similar to those of the nondiabetic heart. On the contrary, treatment with PLC failed to rescue the diabetes-induced changes in the sarcolemmal calcium ATPase.[63]

The effects of PLC in a number of models of CHF are particularly evident under conditions of high-energy demand that is induced by increases in workload. Therefore, it seems likely that PLC is able to correct some metabolic steps of the process that leads to heart failure.

Besides its effect on the heart, PLC could be helpful in CHF for a specific action on peripheral heart muscle. In CHF, exertional fatigue is not simply the result of skeletal muscle underperfusion.[64–67] In most patients, there is a decrease in flow responses to exercise as a result of an abnormality of arterial vasodilatation, evidenced by a failure of leg vascular resistances to decrease during exercise.[65,68] Alterations in mitochondrial population or substrate use also may be responsible for the depressed exercise performance as well as metabolic deconditioning. Interestingly, at rest, the peripheral muscle of patients with CHF does not extract FFA, but only glucose.[69,70] This suggests that impairment of FFA oxidation might be due to a lack of carnitine; or conversely, glucose uptake is enhanced. During moderate exercise, there is an increase of glucose uptake with excessive production of lactate, but no

recruitment of FFA.[37,38] All of these observations, and the positive data obtained by the use of PLC to improve the walking capacities of patients with peripheral arterial disease,[71–75] suggested that PLC could specifically improve metabolism and function of skeletal muscle in patients with CHF.

THERAPEUTIC USE OF PROPIONYL-L-CARNITINE

PLC is used for treatment of cardiovascular diseases. Anand *et al.*[76] studied the effects of acute and chronic administration of PLC (1.5 g/day) on hemodynamics, hormonal levels, exercise capacity, and oxygen consumption in 30 patients with CHF New York Heart Association (NYHA) classes II and III, and LV ejection fraction (EF) less than 40%. There were no changes in the hemodynamics or neurohormonal levels after acute or chronic administration, except for a reduction in pulmonary artery pressure. After 1 month of treatment, however, a significant increase in exercise capacity and peak VO_2 was observed; this suggested a possible improvement of peripheral muscle metabolism.

Another study examined the effects of PLC (15 g/day for 1 month) on limb metabolism, at rest and during exercise.[70] Skeletal muscle metabolism was assessed as femoral arterial venous (A–V) difference for lactate, pyruvate, and FFA. At rest, PLC caused a reduction of arterial and venous blood levels of FFA, but did not change the overall muscle extraction of FFA, lactate, or pyruvate. After maximal exercise, PLC decreased the negative A–V difference for lactate, restored a positive A–V difference for pyruvate, and did not change that for FFA. The investigators concluded that PLC improved skeletal muscle metabolism in patients with idiopathic dilated cardiomyopathy by increasing pyruvate flux into the Krebs cycle and decreasing lactate production. This effect, which occurs in the absence of major hemodynamic and neuroendocrine changes, may underlie the ability of PLC to increase exercise performance in patients with CHF.

Caponnetto *et al.*[77] reported the effects of PLC on 50 patients with mild CHF (NYHA class II) who were symptomatic despite therapy with digitalis and diuretics, with an EF less than 45%. The patients were randomized to receive 1.5 g/day of PLC or placebo orally for 6 months. Maximal exercise time in the treated group was significantly increased (1 min longer vs. placebo), whereas lactate production was significantly reduced. LV shortening fraction and left ventricular ejection fraction (LVEF) showed a significant increase in the group that was given PLC, and systemic vascular resistances lowered. The greatest changes occurred after the first month of treatment and persisted throughout the entire period of treatment. Other authors confirmed similar data.[78] Bachetti *et al.*[79] reported that, when PLC was given to patients with severe heart failure (NYHA IV), it was able to reduce the increase in tumor necrosis factor-α (TNF-α) and, in particular, its soluble receptor that is elevated in CHF,[80–82] and that it is responsible for intracellular signaling of the effects of TNFα. An increased TNF was implicated in the skeletal muscle changes of patients with CHF.[83]

These data have encouraged a multicenter, international study on the effects of PLC on exercise duration.[84] A total of 574 patients under stable mandatory therapy with angiotensin-converting enzyme inhibitors, diuretics, and digitalis were studied. The primary efficacy variable was the maximum exercise test duration on a bicycle; rates of negative outcomes and quality of life were the main secondary variables. A

slight (nonsignificant) difference of 15 s in favor of PLC was noted in the adjusted 6-month means of maximum exercise duration in the completer/compiler population (353 patients: 188 in the PLC group and 165 in the placebo group). In a subgroup of patients with EF between 30% and 40% and baseline exercise duration within 480 s, there was a 57.7-s increase in exercise test duration after PLC administration; this suggested that patients with some degree of deconditioning and relatively preserved myocardial function are likely to benefit from treatment. There are several studies on the effects of PLC in peripheral artery disease, but this is beyond the scope of this review; this topic will be addressed in detail by William Hiatt in this volume.

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