L-Carnitine Treatment for Congestive Heart Failure
—— Experimental and clinical study ——

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To evaluate the therapeutic efficacy of l-carnitine in heart failure, the myocardial carnitine levels and the therapeutic efficacy of l-carnitine were studied in cardiomyopathic BIO 14.6 hamsters and in patients with chronic congestive heart failure and ischemic heart disease. BIO 14.6 hamsters and patients with heart failure were found to have reduced myocardial free carnitine levels (BIO 14.6 vs FI, 287 ± 26.0 vs 384.8 ± 83.8 nmol/g wet weight, $p < 0.05$; patients with heart failure vs without heart failure, 412 ± 142 vs 769 ± 267 nmol/g $p < 0.01$). On the other hand, long-chain acylcarnitine level was significantly higher in the patients with heart failure (532 ± 169 vs 317 ± 72 nmol/g, $p < 0.01$). Significant myocardial damage in BIO 14.6 hamsters was prevented by the intraperitoneal administration of l-carnitine in the early stage of cardiomyopathy. Similarly, oral administration of l-carnitine for 12 weeks significantly improved the exercise tolerance of patients with effort angina. In 9 patients with chronic congestive heart failure, 5 patients (55%) moved to a lower NYHA class and the overall condition was improved in 6 patients (66%) after treatment with l-carnitine. L-carnitine is capable of reversing the inhibition of adenine nucleotide translocase and thus can restore the fatty acid oxidation mechanism which constitutes the main energy source for the myocardium. Therefore, these results indicate that l-carnitine is a useful therapeutic agent for the treatment of congestive heart failure in combination with traditional pharmacological therapy.

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MOST treatment regimens for congestive heart failure involve the use of digitalis, diuretics, catecholamines, and vasodilators. However, excessive administration of catecholamines has been reported as a possible cause of myocardial injury[1-2] In fact it has been demonstrated that β-adrenergic receptor blockade is beneficial in the treatment of dilated cardiomyopathy[3-4] These studies have shown that inotropic stimulation can exacerbate the detrimental effects of a deficit in chemical energy by increasing energy expenditure in an energy-starved heart. Conversely, it seems likely that efforts to reduce the energy expenditure of overloaded myocardium and to improve myocardial energy metabolism could prolong the survival of patients with chronic heart failure.

Thus, it appears to be important in determining the therapeutic efficacy of drugs for use in heart failure to be evaluated with regard to myocardial metabolism, and for the improvement of cardiac metabolism to be a major goal of treatment for chronic heart failure.

It is now apparent that the myocardium in patients with congestive heart failure is not normal, because important structural and molecular changes can be detected in such

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hearts. There is some evidence that defects in myocardial energy metabolism may be present in chronic congestive heart failure, and that inadequate myocardial contractility may be due to a reduction in myocardial oxygen uptake in absolute or relative terms.[5-6]

The major energy source of the heart is fatty acid oxidation, and under conditions of reduced tissue oxygenation, there is a slow-down of the oxidation of fatty acids, with a consequent accumulation of fatty acyl carnitine and CoA in the myocardium. Accumulation of acyl CoA inhibits the action of adenine-nucleotide translocase and thus prevents the transfer of ATP and ADP from the mitochondria to the cytoplasm and vice versa.[7] Long-chain acyl carnitine is an amphiphilic substance and can induce changes in membrane function, such as in enzyme activities and the ion transport systems.[8] Thus, sequestration of ATP within the mitochondria and cell membrane injury both appreciably reduce the energy available to myocytes, and consequently impair the contractile activity of the myofibrils.

Carnitine is an essential cofactor for the transport of long-chain fatty acids across the inner mitochondrial membrane, and alterations in carnitine metabolism may contribute to the pathogenesis of cardiac dysfunction. Tissue carnitine deficiency has been documemted in patients with endocardial fibroelastosis,[9] familial cardiomyopathy,[10] as well as dystrophic cardiomyopathic hamsters,[11] rats with pressure-overload myocardial hypertrophy,[12] and dogs with myocardial ischemia.[13-14] Furthermore, it has been demonstrated that administration of l-carnitine is capable of reversing the inhibition of adenine-nucleotide translocase[15] and accelerating the rate of glycolysis.[16]

Thus, carnitine plays an important role in myocardial energy metabolism and a trial of its therapeutic use seems justified in patients with chronic congestive heart failure. Accordingly, we evaluated the therapeutic efficacy of l-carnitine in chronic congestive heart failure by performing both experimental and clinical studies.

This paper reports the myocardial carnitine concentrations in cardiomyopathic BIO 14.6 Syrian hamster and in patients with chronic congestive heart failure. The therapeutic efficacy of l-carnitine in patients with chronic congestive heart failure and ischemic heart disease, as well as in cardiomyopathic hamsters, is also discussed.

MATERIALS AND METHODS

1. Myocardial carnitine concentration in cardiomyopathic BIO 14.6 Syrian hamsters

We used BIO 14.6 Syrian hamsters, which constitute a well-studied animal model of human congestive cardiomyopathy. This animal develops the following characteristic pathological changes: cardiac myolysis at 30–40 days of age, cardiac hypertrophy at approximately 150 days of age, cardiac dilation at approximately 250 days of age, and frank congestive heart failure at approximately 1 year of age.[17] The animals used as controls were F1 hybrids between the BIO 14.6 hamsters and an unrelated normal line (healthy Golden hamsters).

Hearts were excised at 90 days of age for measurement of free carnitine, short-chain acylcarnitine, and long-chain acylarnitine levels. Free carnitine was determined enzymatically using carnitine palmitoyltransferase by modification of the method of Marquis and Fritz,[18] as described previously.[19] Short-chain acylcarnitine and long-chain acylcarnitine were assayed as free carnitine, using alkaline hydrolysis performed using the method of Pearson et al.[20] The results were expressed as the mean±SD of the concentration per wet tissue weight.

2. Myocardial carnitine concentration in patients with chronic congestive heart failure

Biopsy specimens of left ventricular apillary muscles were obtained from eight patients (average age: 51.9±6.9 years; range: 39 to 60 years) undergoing valve replacement surgery because of chronic heart failure due to mitral valve disease (isolated mitral stenosis in 3 cases, isolated mitral regurgitation in 2 cases, and combined mitral stenosis and regurgitation in 3 cases). As a control, seven autopsy specimens were obtained from age-matched patients (average age: 59.3±11.2 years; range: 42 to 70 years) without a history of heart disease or heart failure (malignant lymphoma in 3 cases, leukemia in 1 case, and other cancers in 3 cases). In the control group, left ven-

tricular papillary muscle biopsies were obtained within 4 h after death and stored in liquid nitrogen.

The measurement of free carnitine, long-chain acylcarnitine, and short-chain acylcarnitine was performed as mentioned above and the results were expressed as the mean±SD of the concentration per wet tissue weight.

3. Effect of l-carnitine on myocardial histological appearance in BIO 14.6 hamsters

Cardiomyopathic BIO 14.6 Syrian hamster at 20 days of age were divided into 2 groups and treated as follows: The control group had 1 ml of saline solution injected intraperitoneally daily for 70 days (n=7), while the l-carnitine group had 300 mg/kg of l-carnitine injected intraperitoneally daily for 70 days (n = 9). In the control group, 2 BIO 14.6 hamsters died during the experiment. All surviving hamsters (control group: 5; l-carnitine group: 9) were killed by cervical dislocation at 90 days of age.

A morphometric method was used to measure the degree of protection against myocardial damage. The total myocardial area and the area of damaged myocardium (necrosis, fibrosis, and calcification) were measured and the proportion of damaged myocardium was compared between the 2 groups. Hearts were sliced transversely at the midpoint of the ventricle. Sections of 3 μm in thickness were stained with hematoxylin and eosin, Mallory-Heidenhain triple stain, and von Kossa's stain for calcium salts. Photographs ($\times 60$ magnification) were taken of the 3 differently stained slides. The damaged and total myocardial areas on each slice were then traced out and measured using an image analyser system. The extent of necrosis, fibrosis, and calcification was measured separately for each damaged area, and the proportion of these types of damage compared between the 2 groups. Results were expressed as the mean±SE.

4. Effect of l-carnitine on exercise tolerance in patients with angina pectoris

Twelve patients (10 men and 2 women) were entered into this study. Their average age was 56.8±2.5 years (range: 43 to 70 years). The requirements for inclusion were as follows: 1) definite electrocardiographic evidence of myocardial ischemia (i.e., 1 mm or more of horizontal or down-sloping ST depression during an exercise test, 2) the presence of a definable ischemic end-point during exercise testing due to anginal pain, 3) no evidence of rest angina, 4) no evidence of valvular heart disease, cardiomyopathy, or conduction disturbances like bundle branch block, and 5) no digitalis treatment for at least 1 month prior to this study. Patients with unstable angina or recent myocardial infarction (within 6 months) were excluded from this study. Seven patients had old myocardial infarction and 8 underwent coronary angiography.

Exercise testing was carried out using a treadmill test. The speed and the elevation of the slope were increased every 3 min. The initial stage was 1.7 miles/h at a 0% gradient (stage 0) and the next was 1.7 miles/h at a 5% gradient (stage 1/2). When stage 1/2 was completed, the test was continued using the conventional Bruce protocol. Neither ST depression nor a target heart rate was used as an indication for stopping the test, and patients continued until the onset of angina, at which time they stopped exercising. During treadmill testing, the ECG was monitored using leads aVf, V_1, and V_5. The heart rate and blood pressure were recorded at the end of each stage of the exercise test at well as while the patient was standing at rest. Exercise tests were performed before and after the placebo treatment period and at 4 and 12 weeks after the begining of l-carnitine treatment. Each exercise test (a total of 4) was performed at approximately the same time of day.

The treatment schedule was as follows: during the first 4 weeks all patients received a placebo and then they received l-carnitine at a daily dose of 900 mg (300 mg t.d.s.) for a period of 12 weeks. During the study, all patients continued to use sublingual nitroglycerin at the onset of angina, but all other antianginal drugs were discontinued.

Significant differences were assessed between the exercise time, the time to onset of ST depression of 1 mm, the heart rate, and the pressure-rate product before and after treatment with the placebo as well as between the placebo period and treatment with l-carnitine. Results were expressed as the mean±SE.

5. Therapeutic efficacy of l-carnitine in patients with chronic congestive heart

TABLE I HISTOLOGICAL EFFECT OF TREATMENT WITH L-CARNITINE IN BIO14.6 HAMSTERS

Myocardial histology	Saline-treated group (n=5)	l-carnitine-treated goup (n=9)
Total damage area:		
Per 10^{-2} mm^2	192.0 ± 33.7	$61.9 \pm 19.4^{\#\#}$
%	8.18 ± 0.66	$2.70 \pm 0.68^{\#\#}$
Area of necrosis:		
Per 10^{-2} mm^2	16.4 ± 7.8	15.6 ± 5.8
%	0.54 ± 0.26	0.65 ± 0.23
Area of fibrosis:		
Per 10^{-2} mm^2	104.2 ± 9.4	$29.4 \pm 7.2^{\#\#}$
%	4.63 ± 0.56	$1.22 \pm 0.23^{\#\#}$
Area of calcification:		
Per 10^{-2} mm^2	45.2 ± 14.7	$16.8 \pm 7.7^{\#}$
%	1.90 ± 0.50	$0.66 \pm 0.28^{\#}$

Values are expressed as the mean $\pm$ SD. $^{\#\#}p<0.01$ and $^{\#}$ $p<0.05$ compared with the saline-treated group. % means the proportion of each damaged area.

TABLE II MYOCARDIAL LEVELS OF CARNITINE AND ITS DERIVATIVES IN PATIENTS WITH AND WITHOUT HEART FAILURE

Patients	Free Carnitine (n mol/g)	Short-Chain Acylcarnitine (n mol/g)	Long-Chain Acylcarnitine (n mol/g)	Total Carnitine (n mol/g)
heart failure (n=8)	$412 \pm 142^{**}$	377 ± 163	$532 \pm 169^{**}$	1321 ± 170
without heart failure (n=7)	769 ± 267	228 ± 144	317 ± 72	1315 ± 377

Values are expressed per gram of wet tissue weight and represented as the mean $\pm$ SD. $^{**}=p<0.01$, heart failure VS without heart failure.

failure

The trial included 9 patients (4 men and 5 women, average age: 69.0 ± 7.4 years, range: 22 to 80 years). All patients were taking digitalis and diuretics for congestive heart failure (NYHA classes II-IV) due to ischemic heart disease (4 cases), valvular heart disease (3 cases), or cardiomyopathy (2 cases).

The initial clinical condition was assessed on the basis of the following parameters: body weight, heart rate, arterial blood pressure, resting and exercise dyspnea (present or absent), hepatomegaly (cm from costal arch), and peripheral edema (present or absent). ECG and chest X-ray examinations were performed before, and at 8 weeks after, the begining of l-carnitine treatment. Elevation of cardiac kinetics was performed before and at the end of treatment by means of 2-dimentional echocardiography.

On entry to this study, each patient was receiving digitalis, diuretics and, when necessary, vasodilators or anti-arrhythmic agents. The administration of these drugs was continued during the study without changing the dose or the agents in use. All patients were given a placebo for 2 or 4 weeks and then received l-carnitine at a daily dose of 900 mg (300 mg t.d.s.) for a period of 8 weeks. All results were expressed as the mean $\pm$ SD.

6. Statistical analysis

Data were analysed using Student's t-test for the parametric and nonparametric variables. P values of less than 0.05 were considered significant changes.

RESULTS

I: Effects of l-carnitine in BIO 14.6 hamsters
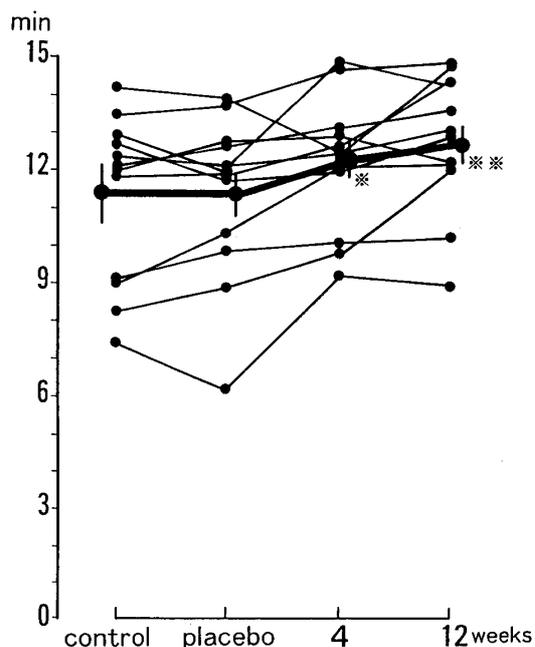
1. Myocardial carnitine concentration

Fig.1. Effect of 1-carnitine on the duration of exercise.
Values are expressed as the mean±SE.
**p<0.01 and *p<0.05 compared with the exercise during the placebo period.

The free carnitine concentration in BIO 14.6 hamsters was significantly lower than in the control F1 hamsters (287.0±26.0 vs 384.8±83.8 nmol/g wet weight, p<0.05). The short-chain acylcarnitine concentration in BIO 14.6 hamsters was also significantly lower than in the control F1 hamsters (197.0±56.0 vs 425.2±54.8 nmol/g wet weight, p<0.01). On the other hand, there was no significant difference in the concentration of long-chain acylcarnitine between the BIO 14.6 and F1 hamsters (183.6±82.8 vs 213.6±58.0 nmol/g wet weight). The total carnitine concentration in BIO 14.6 hamsters was significantly lower than in the control F1 hamsters (667.6±136.4 vs 1023.6±81.4 nmol/g wet weight, p<0.01). Thus, the cardiomyopathic hamsters had a reduced myocardial carnitine concentration.

2. Effect of l-carnitine on myocardial histological appearance

Table I shows the areas of necrosis, fibrosis, and calcification in the hearts of the 2 groups of hamsters. The total and the percentage of the damaged area in the l-carnitine treated group were both significantly decreased compared with the saline-treated group. The total and percentage areas of necrosis in the l-carnitine group were not significantly different from those in the saline group, but the total and percentage areas of fibrosis and calcification were significantly smaller in the l-carnitine group. Thus, the administration of exogenous l-carnitine was effective in protecting the myocardium of BIO 14.6 hamsters against damage.

II: Effects of l-carnitine in patients with heart failure or angina pectoris

1. Myocardial carnitine concentration in patients with chronic congestive heart failure

Preliminary postmortem study of the changes in the levels of free carnitine and its derivatives showed that human autopsy specimens obtained within 4h after death did not develop significant alterations in the concentration of myocardial free carnitine or its derivatives.

Table II shows the myocardial concentrations of free carnitine and its derivatives in patients with and without chronic heart failure. The mean myocardial free carnitine concentration in the patients with heart failure was significantly lower than in the patients without heart failure. On the other hand, the mean myocardial long-chain acylcarnitine level was significantly higher in heart failure. The mean myocardial short-chain acylcarnitine and total carnitine levels in heart failure were not significantly different from the control values.

Thus, we found a decrease in the myocardial free carnitine concentration and an increase in the long-chain acylcarnitine concentration in patients with chronic congestive heart failure, as was previously shown in patients with ischemic heart disease.

2. Effect of l-carnitine on exercise tolerance in angina pectoris

The mean exercise times were respectively 11.4±0.6 min and 11.4±0.7 min during the control and placebo treatment periods. With l-carnitine treatment, the exercise time significantly increased to 12.2±0.5 min after 4 weeks of treatment (p<0.05) and to 12.8±0.5 min after 12 weeks (p<0.01) (Fig. 1).

The time required for the appearance of 1 mm of ST depression was respectively 6.3±0.9 min and 6.4±0.9 min during the control and placebo treatment periods. With

l-carnitine treatment, ST segment changes showed no significant improvement at 4 and 12 weeks.

The mean maximal ST index [the calculated ST depression (mV) plus the ST slope (mV/sec)] was -2.6 ± 0.2 and -2.9 ± 0.3, respectively, during the control and placebo treatment periods. With l-carnitine treatment, the ST index was respectively -2.7 ± 0.3 and -3.1 ± 0.6 after 4 and 12 weeks of treatment. It showed no significant improvement at maximal load work after 4 and 12 weeks of treatment, but the index at the same load work showed a significant improvement after 12 weeks of treatment ($p<0.05$). At Bruce grade I, the mean ST index was -1.7 ± 0.3 and -1.8 ± 0.3 during the control and placebo treatment periods, while l-carnitine treatment reduced it to -1.2 ± 0.3 and -1.0 ± 0.3 after 4 and 12 weeks, respectively (both $p<0.05$). At Bruce grade II, the mean ST index was respectively -2.5 ± 0.6 and -2.6 ± 0.6 during the control and placebo periods, while l-carnitine treatment reduced it to -1.8 ± 0.5 and -1.7 ± 0.5 after 4 and 12 weeks (both $p<.05$).

The mean heart rate achieved at the termination of exercise was 125.8 ± 6.0 beats/min and 126.7 ± 5.8 beats/min, respectively, during the control and placebo treatment periods. Mean maximal heart rates at the termination of exercise was 130.0 ± 6.4 beats/min and 132.9 ± 5.8 beats/min after 4 and 12 weeks of l-carnitine treatment respectively, showing no significant difference.

The mean maximal pressure-rate product achieved at the termination of exercise was respectively 17310 ± 2070, 18000 ± 1550, and 17920 ± 2030 during the placebo period, after 4 weeks, after 12 weeks of l-carnitine treatment. There was no significant difference among these values.

3. Therapeutic efficacy of l-carnitine for chronic congestive heart failure

Table III shows the NYHA class, heart rate, body weight, cardiothoracic ratio, ejection fraction, and improvement of general condition recorded at baseline and after 8 weeks of treatment with l-carnitine. Five patients (55.5%) moved to a lower NYHA category after treatment with l-carnitine for 8 weeks. Echocardiographic examination showed changes in the ejection fraction in 4

TABLE III CAHNGES IN CLINICAL AND OTHER PARAMETERS AND IN NYHA CLASS IN HEART FAILURE PATIENTS TREATED WITH L-CARNITINE

No.	sex	age	Diagnosis	NYHA		Heart rate		Body weight (kg)		CTR (%)		EF (%)		Overall improvement
				before	after	before	after	before	after	before	after	before	after	
1	F	80	IHD	III	II	68	66	42	42	68	62	58	58	(+)
2	F	65	MR	II	II	66	72	41	42	53	53	60	58	(−)
3	M	73	IHD	II	II	72	84	43	43	67	66	48	56	(+)
4	F	64	MRS	III	II	72	66	30	29	71	67	56	56	(+)
5	F	66	IHD	II	II	84	83	55	55	65	64	50	62	(+)
6	M	59	IHD	IV	II	92	84	45	43	57	57	46	48	(+)
7	F	80	CM	III	II	62	62	47	46	56	51	57	58	(+)
8	M	73	MR	III	II	96	75	48	46	72	72	57	68	(+)
9	M	22	DCM	III	III	92	90	68	68	63	63	32	32	(−)

IHD; Ischemic heart disease, MR; Mitral valve regurgitation, MRS; Mitral valve regurgitation and stenosis, CM; Cardiomyopathy due to doxorubicin, DCM; Dilated cardiomyopathy. (+) shows an improvement in overall patient condition.

patients (44.4%). Exertional dyspnea was relieved in 4 patients (44.4%) and pedal edema disappeared in 3 patients (33.3%).

The overally improvement of patients was evaluated by considering the changes in findings plus the alleviation of symptoms, and an overally improvement was seen in 6 patients (66.6%). Most of the laboratory variables did not change with l-carnitine treatment.

DISCUSSION

BIO 14.6 cardiomyopathic hamsters and patients with chronic congestive heart failure were found to have reduced myocardial free carnitine levels. On the other hand, the long-chain acylcarnitine concentration was significantly higher in patients with chronic heart failure.

Regitz et al[21] reported that a decrease in myocardial free carnitine was a relatively consistent finding in both patients with idiopathic dilated cardiomyopathy and coronary insufficiency. Pierpont et al[22] however, demonstrated that only 7 of 51 patients with congestive heart failure had low total myocardial carnitine levels and these levels did not corelate with any hemodynamic variables. They measured only total carnitine concentrations and total carnitine includes free carnitine, short-chain acylcarnitine, and long-chain acylcarnitine. Since it was demonstrated that the reduction of free carnitine induced the accumulation of long-chain acylcarnitine, measurement of the total carnitine level itself does not indicate real changes in tissue carnitine metabolism. Therefore, we suggest that the difference in results between our study and that of Pierpont et al[22] may be due to this point.

Carnitine of dietary or endogenous origin is released into the blood and is taken up by skeletal muscle and cardiac muscle. Waber et al[10] have reported that defective carnitine transport in the kidney and possibly in the gut is a likely cause of human systemic carnitine deficiency. York et al[11] suggested that reduced myocardial carnitine levels in BIO 14.6 hamsters might result from impaired transport of carnitine into the myocytes due to an altered cardiac carnitine binding protein. However, reduced myocardial carnitine levels were not only found in patients with dilated cardiomyopathy and coronary

artery disease, but also in patients with cardiac failure due to valvular heart disease. It may be supposed, therefore, that myocardial carnitine loss represents a nonspecific change in patients with heart failure.

Since free carnitine is a cofactor in the system which transports long-chain fatty acids across the inner mitochondrial membrane, reduction of the free carnitine impairs the mitochondrial oxidation of fatty acids and leads to lipid accumulation in the cytosol. Since the heart muscle depends on the oxidation of fatty acids for most of its energy, the heart would be expected to be the organ most severely affected by a relative or absolute carnitine deficiency. In fact, in animal models and humans, reduction of the myocardial free carnitine level causes secondary biochemical changes and functional impairment[9-14]

Long-chain acyl CoA and long-chain acylcarnitine increase in the ischemic myocytes. Long-chain acyl CoA inhibits the activity of adenine nucleotide translocase, an important enzyme located in the inner mitochondrial membrane which transfers ATP synthetized in the mitochondria to the outside[7] Long-chain acylcarnitine is an amphiphilic substance and can induce major changes in membrane function through the insertion of free amphiphile molecules into the membrane lipid bilayer via a detergent-like effect.[8,28] The accumulation of such molecules has been suggested as a cause of cellular damage in the ischemic heart.

It is now apparent that various defects of myocardial energy metabolism may be present in chronic heart failure. Endomyocardial biopsies taken from the hearts of patients with chronic heart failure have shown a correlation between a decrease in the ATP concentration and impairment of myocardial contraction and relaxation[23] Morphometric studies of the hypertrophied and failing heart have shown that the number of transverse capillary profiles per mm^2 is decreased, so that the intercapillary distance is increased in such hearts[24] These findings suggest that failing hearts may be operating under conditions of relative anaerobiosis.

It is of interest that we found that patients with chronic congestive heart failure have not only a loss of free carnitine but also an increased level of long-chain acylcarnitine in

the myocardium. The addition of l-carnitine to mitochondrial preparations can lessen the inhibitory effect of long-chain acyl CoA on adenine nucleotide translocase and can reduce the accumulation of long-chain acylcarnitine in the ischemic heart. Therefore, the therapeutic use of l-carnitine seems justified in situations in which there is a myocardial oxygen uptake deficiency and/or depressed oxidation of fatty acids.

Myocardial damage in BIO 14.6 hamsters, which have depressed oxidation of fatty acids,[29] was prevented by the intraperitoneal administration of l-carnitine in the early stage of cardiomyopathy. Oral administration of l-carnitine for 12 weeks improved the exercise tolerance of patients with effort angina. All patients underwent exercise testing twice during a 4 week observation period, and showed no change in the duration of exercise or the time to the onset of ischemic ST changes. Therefore, the improvement observed after 4 and 12 weeks of l-carnitine treatment was not due to training or a placebo effect. Yoshitoshi et al[25] investigated the efficacy of l-carnitine for ischemic heart disease in a double-blind multicenter trial. The maximal exercise duration and the time to onset of 1 mm of ST depression were both significantly prolonged in the l-carnitine group compared to pretreatment levels. Thus, their study also showed that l-carnitine is a clinically useful drug for the treatment of ischemic heart disease.

We investigated the effect of l-carnitine administration in 9 patients suffering from chronic congestive heart failure. Evaluation of cardiac kinetics using echocardiography did not show any significant improvement at the end of treatment with l-carnitine, but 5 patients (55%) moved to a lower NYHA class and the overall condition was improved in 6 patients (66%) after treatment. Ghidini et al[26] have reported on the therapeutic efficacy of l-carnitine in elderly patients suffering from heart failure. They found a distinct improvement in both subjective and objective parameters: heart rate was reduced, diuresis was increased, and reductions were observed in dyspnea, peripheral edema and jugular venous pressure. All patients moved down to a lower NYHA class. However, there was no significant improvement in a number of echocardiographic para-

meters. This points out that the effect of l-carnitine was nevertheless substantial, as shown by the faster and more marked reduction in digoxin consumption in the patients treated with the drug compared to those treated with placebo. Since l-carnitine has neither a positive inotropic action nor a vasodilating action, it may be difficult to expect an improvement of cardiac kinetic parameters due to treatment with l-carnitine.

The mechanism of action by which l-carnitine produces its effect may be regarded as "physiological", in that it promotes energy production by cardiac myocytes. In contrast, positive inotropic agents produce a marked increase in contractility and an increase in heart rate, with a resulting increase of myocardial oxygen consumption. It is apparent that the myocardium has structural and molecular changes in congestive heart failure, and is in a condition of energy starvation. Therefore, the possibility is raised that therapeutic measures which increase energy expenditure may hasten the clinical deterioration so often seen in congestive heart failure![-2] Conversely, efforts to reduce energy expenditure and/or improve energy metabolism may prolong survival in patients with congestive heart failure[30] Katz[27] pointed out that a reduction of energy expenditure should be a major goal of therapy in the management of congestive heart failure.

L-carnitine is capable of reversing the inhibition of adenine nucleotide translocase and thus can restore the fatty acid oxidation mechanism which constitutes the main energy source for the myocardium. It appears to be a useful therapeutic agent for the treatment of congestive heart failure in conjunction with traditional pharmacological therapy. Further clinical studies should be undertaken to elucidate the metabolic and functional consequences for the myocardium of l-carnitine treatment in heart failure.

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