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Effect of propionyl-l-carnitine and enalapril on cardiac function of pressure-overloaded rats during increase in load

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Abstract

Chronic administration of propionyl-l-carnitine has been recently shown to correct hypertrophy related abnormalities in muscle mechanics. Accordingly, this study investigated whether the drug would similarly improve cardiac dynamics in rats with pressure overload. Enalapril was used for comparison. Drugs were administered in the drinking water for 3 weeks to Wistar Kyoto rats with a 2 week abdominal aortic constriction. Cardiac function was studied under urethane anaesthesia in basal conditions, during increase in preload, and during increase in afterload. Basal cardiac function was comparable in pressure-overloaded and sham-operated animals. Neither propionyl-l-carnitine nor enalapril affected the basal performance. Compared to sham-operated animals, untreated pressure-overloaded rats showed an impaired cardiac response (cardiac output, stroke volume) to preload increase induced by saline i.v. infusion. Propionyl-l-carnitine dose dependently improved cardiac function in the range 30–180 mg/kg, without affecting cardiac hypertrophic growth. Enalapril (3 mg/kg) reduced cardiac hypertrophy and improved cardiac function. The two effects were unrelated. The afterload increase by total aortic occlusion evidenced a reduction in the left ventricle pressure generating capacity of hypertrophied hearts. Propionyl-l-carnitine did not modify this parameter, while enalapril afforded a significant improvement. Results show that propionyl-l-carnitine significantly improves in vivo cardiac dynamics under conditions of increased energy demand. The effect is not due to inotropic efficacy, but presumably to increased cardiac efficiency.

Keywords: Propionyl-l-carnitine; Pressure overload; Cardiac hypertrophy; Enalapril; Cardiac function

1. Introduction

Propionyl-l-carnitine is a natural compound that modulates energy substrate metabolism in the heart and skeletal muscle (Corsico et al., 1993; Paulson et al., 1986; Siliprandi et al., 1991). It mediates mitochondrial fatty acid transport and replenishes citric acid cycle intermediates (Tassani et al., 1994). In this respect, propionyl-l-carnitine constitutes the prototype of a class of pharmacological agents acting through a novel mechanism of action. For its anaplerotic properties propionyl-l-carnitine is currently being investigated as an additional therapeutic agent in patients with left ventricular dysfunction associated with heart failure and with coronary disease (Bartels et al., 1994; Caponnetto et al., 1994).

The efficacy of propionyl-l-carnitine has been proved in a number of experimental models, including heart failure due to coronary artery ligation (Micheletti et al., 1993), volume overload (El Alaoui-Talibi and Moravec, 1993) and pressure overload (Yang et al., 1992; Micheletti et al., 1994). It is therefore likely that different mechanisms of action underlie the pharmacological effects seen with propionyl-l-carnitine in such different pathological conditions. In particular, there is evidence that the acute and chronic effects of propionyl-l-carnitine may differ. In fact, acute administration of propionyl-l-carnitine has resulted in: (1) stimulation of fatty acid oxidation in myocardium homogenate (Paulson et al., 1986) and of glucose oxida-

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tion in the working hypertrophied heart (Schönekess et al., 1995); (2) increase of ATP/ADP ratio and creatine phosphate content in isolated myocytes from pressure-overloaded heart (Torielli et al., 1995); (3) increase of shortening velocity and peak shortening in myocytes isolated from infarcted hearts (Li et al., 1995). Despite these prominent in vitro effects, the acute administration of propionyl-l-carnitine failed to affect the cardiac output of conscious pressure-overloaded rats (Yang et al, 1992). A chronic treatment with propionyl-l-carnitine to pressure-overloaded rats, beside reducing the prolongation in the contraction time course of papillary muscles and the slowing of the shortening velocity of skinned trabeculae, maintained the relative proportion of myosin heavy chain isoforms of left ventricular wall (Micheletti et al., 1994). It was therefore of interest to investigate whether the normalisation of papillary muscle mechanics and isoenzyme content afforded by propionyl-l-carnitine would be reflected by an in vivo improvement of cardiac dynamics in pressure-overloaded rats. Since angiotensin converting enzyme inhibition has been shown to improve ventricular function in pressure overload (Weinberg et al., 1993), enalapril was used for comparison.

2. Materials and methods

2.1. Animals

Male Wistar-Kyoto rats (Charles River, Calco, Italy) weighing 200–250 g were used. Under pentobarbital (50 mg/kg i.p.) anaesthesia, a silver clip of 0.8 mm diameter was placed around the abdominal aorta, above the renal arteries, as previously described (Yang et al, 1992). Sham-operated animals underwent the same surgical procedure, with the exception that the clip was not fixed into place.

5 weeks later, under urethane anaesthesia (1.5 g/kg i.p.), the animals were placed on a heating pad (Homeothermic Blanket, Harvard, South Natick, MA), and the left femoral artery and the right carotid artery were cannulated with a microtip pressure transducer catheter (PR 448, Millar Instruments, Houston, TX) and a PE 50 attached to a Gould P23XL pressure transducer (Gould, Cleveland, OH), respectively, to monitor arterial blood pressure distal and proximal to the aortic constriction.

2.2. Left ventricular function

Left ventricular function was assessed at rest, during increased preload, and during increased afterload. Animals were ventilated by a positive pressure respirator (Harvard Rodent Respirator Mod. 683, South Natick, MA), a left thoracotomy was performed and a flow probe (Transonic 3 SB, Ithaca, NY) was placed around the ascending aorta to monitor aortic blood flow (cardiac output). Thereafter, one PE 50 catheter was advanced into the right atrium via the right jugular vein to monitor right atrial pressure, and one was inserted into the left jugular vein to deliver the saline preload. When basal parameters had stabilised, preload was increased by infusing into the left jugular vein 40 ml/kg per min warm (37°C) physiological solution (0.9% NaCl) for 1 min. The maximum value of aortic flow after the onset of infusion was taken as the maximum pumping ability of each heart (peak cardiac output). Haemodynamic parameters during increased preload were taken at the time of peak cardiac output. After approximately 15 min, when the haemodynamic variables returned to baseline, the aortic flowmeter was removed and the carotid catheter was advanced into the left ventricular chamber. Afterload was abruptly increased by totally occluding the aorta for a 5 s period with a snare placed 3–5 mm from its origin.

Pressure transducers were connected to an electrostatic chart recorder (RS 3800, Gould, Cleveland, OH). The analog signals were fed to an AST 386 computer and analysed by IDAS software (Mangoni, Pisa, Italy).

Only rats that did not show overt signs of cardiac failure (hydrothorax) were studied.

Lastly, the heart was removed, rinsed in saline and blotted dry. The atria were excised free, the right ventricle was separated at the septal border so that the interventricular septum remained with the left ventricle, and wet weights determined.

2.3. Treatment

Drugs were administered in the drinking water for 21 days, from the second week after aortic constriction to the day of experiment. Drug concentration was adjusted to body weight on a weekly basis. A preliminary evaluation of water consumption showed that neither drug affected it. The calculated daily intake was: 30, 60, 180 mg/kg for propionyl-l-carnitine · HCl; 1, 3 mg/kg for enalapril maleate. All drugs were obtained from Sigma-tau (Pomezia, Italy).

2.4. Data analysis

Data are expressed as means ± S.E.M. Comparison between sham and clip animals was done by unpaired Student's t-test. Comparisons within each group were done by paired Student's t-test, among groups were done by one-way analysis of variance (ANOVA) followed by Bonferroni/Dunn test. A regression analysis was performed on propionyl-l-carnitine and enalapril groups to show dose dependency. A P value ≤ 0.05 was taken as significant.

3. Results

3.1. Characteristics of aortic constricted animals

The reduction of the abdominal aorta diameter resulted in cardiac hypertrophy, characterised by a significant increase in the weight of left ventricle (+70%), right ventricle (+46%) and atria (+89%; all, $P < 0.01$ vs. sham; Table 1). Propionyl-l-carnitine administered to clip animals did not affect the cardiac hypertrophic growth, as shown by data relative to the highest dose studied (180 mg/kg, Table 1). Conversely, 3 mg/kg enalapril reduced cardiac hypertrophy to a significant extent (Table 1), despite heart weights in this group being noticeably scattered.

3.2. Basal haemodynamics of aortic constricted animals

The mean basal value of systemic systolic blood pressure in clip animals was 53 mmHg higher than in sham animals ($P < 0.01$, Table 2) under closed chest conditions and remained significantly greater ($P < 0.01$) despite some decrease after opening the chest (Table 2). It should be noted that the relatively low pressure values seen in this study are due to urethane anaesthesia. In fact, separate measurements in conscious clip rats yielded a mean carotid systolic pressure value of 220 ± 11 mmHg ($n = 5$), when measured 4 h after catheter implantation under ether anaesthesia.

A mean transstenotic systolic gradient of 36 ± 5 mmHg was observed between carotid and femoral pressures in clip animals, while in sham animals the two measurements did not differ (not shown). A significant transstenotic pressure gradient was present in clip animals from all experimental groups.

Basal haemodynamic parameters of sham and untreated clip rats did not differ, except for total periph-

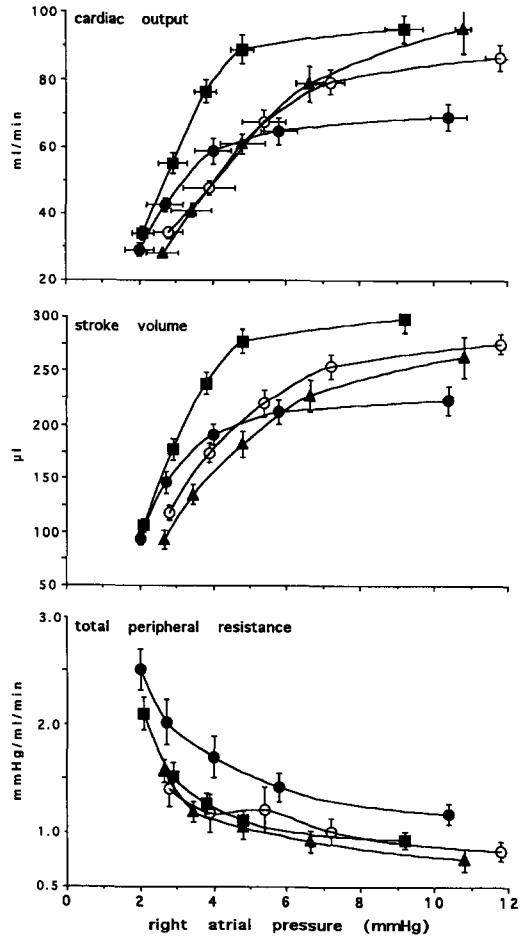

Fig. 1. Cardiac function (cardiac output and stroke volume) and total peripheral resistance in relation to right atrial pressure (RAP), before (leftmost point) and at 10, 20, 30, 60 s of i.v. infusion of physiological solution to increase preload. Data represent the means ± S.E. of sham (○, $n = 9$), untreated pressure overloaded (●, $n = 14$), 180 mg/kg propionyl-l-carnitine (■, $n = 12$) and 3 mg/kg enalapril (▲, $n = 12$) treated rats. Note that S.E. values for RAP are shown only in the upper panel, being the same in the three panels.

Table 1
General characteristics of untreated sham and clip animals and of clip animals treated with the drugs under study

	Sham	Clip	Clip	Clip		ANOVA
	No treatment	No treatment	PLC	Enalapril		P
			180 mg/kg	1 mg/kg	3 mg/kg	
Body weight (g)	322 ± 6	318 ± 8	328 ± 9	330 ± 17	330 ± 6	n.s.
Heart weight (mg)	897 ± 24	1491 ± 56 [a]	1471 ± 49 [b]	1480 ± 58 [b]	1157 ± 52 [b,c,d,e]	< 0.0001
Left ventricle weight (mg)	660 ± 18	1123 ± 33 [a]	1125 ± 34 [b]	1161 ± 43 [b]	870 ± 45 [b,c,d,e]	< 0.0001
Right ventricle weight (mg)	181 ± 6	265 ± 19 [a]	259 ± 12 [b]	221 ± 10	216 ± 12	< 0.001
Atrial weight (mg)	55 ± 1	104 ± 12 [a]	87 ± 7	98 ± 12	71 ± 5	< 0.005
Left ventricle weight/tibia length (mg/cm)	164 ± 4	286 ± 9 [a]	284 ± 8 [b]	290 ± 9 [b]	218 ± 11 [b,c,d,e]	< 0.0001
Right ventricle weight/tibia length (mg/cm)	45 ± 2	68 ± 5 [a]	65 ± 3 [b]	55 ± 2	54 ± 3	< 0.0005
n	9	14	12	7	12	

PLC = propionyl-l-carnithine. [a] $P < 0.05$ by Student's t-test. [b] Different from sham; [c] different from clip; [d] different from PLC 180; [e] different from enalapril 1 by post-hoc (Bonferroni-Dunn) test. Values are means ± S.E.M.

Table 2
Haemodynamic parameters of anaesthetised rats under closed chest and open chest conditions

	Closed chest		Open chest							
	Systolic carotid pressure (mmHg)	Heart rate (beats/min)	Systolic carotid pressure (mmHg)	Heart rate (beats/min)	Cardiac output (ml/min)	Stroke volume (μl)	Cardiac index (ml/kg per min)	Stroke index (ml/kg per min)	TPR (mmHg/ml per min)	n
Sham	72 ± 3	287 ± 12	68 ± 5	296 ± 12	34 ± 3	118 ± 12	106 ± 7	364 ± 34	1.40 ± 0.16	9
Clip	125 ± 11 [b] (n = 7)	291 ± 12	107 ± 6 [b]	317 ± 12	29 ± 2	94 ± 7	92 ± 5	297 ± 21	2.51 ± 0.19 [b]	14
Clip + PLC 180 mg/kg	105 ± 7 (n = 7)	300 ± 15	107 ± 7 [b]	322 ± 10	34 ± 2	106 ± 6	105 ± 6	324 ± 17	2.10 ± 0.15 [b]	12
Clip + enalapril 3 mg/kg	113 ± 8 [b]	306 ± 18	71 ± 4 [a,c,d]	309 ± 14 (n = 11)	28 ± 1	93 ± 9 (n = 11)	85 ± 4	281 ± 24 (n = 11)	1.57 ± 0.11 [c,d]	12
ANOVA (P)	< 0.001	n.s.	< 0.0001	n.s.	< 0.05	n.s.	< 0.05	n.s.	< 0.0001	

[a] P < 0.001 vs. closed chest (paired Student's t test). [b] Different from sham; [c] different from clip; [d] different from PLC by post-hoc (Bonferroni-Dunn) test. Each value is the mean ± S.E.M. of the number of animals shown in the last column (n) except where otherwise indicated.

eral resistance (calculated as the ratio between mean arterial pressure and cardiac output), which was obviously greater in the latter (Table 2 and Fig. 1). Propionyl-l-carnitine treatment did not affect the basal haemodynamic parameters of clip rats at any dose tested, as shown in Table 2 by data relative to the highest dose studied, 180 mg/kg.

Enalapril at 3 mg/kg significantly reduced carotid blood pressure under open chest conditions, unlike that observed in the other experimental groups (Table 2), while basal cardiac output and stroke volume were not affected. Thus, total peripheral resistance was also significantly reduced (Table 2 and Fig. 1).

3.3. Effects of increasing preload and afterload on haemodynamics

The acute increase in cardiac preload induced by saline infusion was monitored by measuring right atrial pressure, which increased to a similar extent in both sham and untreated clip animals (from 2.8 ± 0.45 to 11.8 ± 0.38 and from 1.97 ± 0.39 to 10.4 ± 0.52, respectively). During this procedure, the carotid blood pressure of clip animals rose to significantly higher values than in the sham group (146 ± 7 vs. 100 ± 5 mmHg; $P < 0.05$). Moreover, in the former group only, carotid blood pressure increased dramatically more than did femoral blood pressure, so that the transstenotic pressure gradient rose to 72 ± 6 mmHg; no difference between femoral and carotid pressure was observed during the same procedure in sham animals.

The maximum flow generating capacity (peak cardiac output) observed in clip animals was significantly less than in sham animals: 71.4 ± 3.6 vs. 89.1 ± 4.9 ($P = 0.007$); moreover, peak cardiac output was reached earlier in the clip group, after 46 ± 4 s of infusion compared to 54 ± 3 s in sham animals, although this difference was not statistically significant. Since the increase in preload did not significantly modify heart rate, stroke volume in clip animals was increased to a significantly lower extent: the calculated stroke volume value at peak cardiac output was (μl): 252 ± 18 in clip rats and 280 ± 16 in sham rats ($P < 0.05$). Basal values for cardiac output, stroke volume and total peripheral resistance, and their changes during saline infusion are illustrated in Fig. 1, together with those from rats receiving the highest doses tested of propionyl-l-carnitine (180 mg/kg) and enalapril (3 mg/kg).

3.4. Effect of treatments

Propionyl-l-carnitine treatment in the range 30–180 mg/kg significantly improved the haemodynamic response of clip animals to saline infusion. A dose-dependent relationship was evidenced for both cardiac output and stroke volume (regression significance: $P =$ 0.04 and 0.02, respectively), as illustrated in Fig. 2. Cardiac index and stroke index were also dose dependently increased (regression $P = 0.02$, both; not shown). These effects were seen in the presence of a maximum increase in carotid blood pressure comparable with that of untreated clip animals (159 ± 11 mm Hg). Thus, the fall of total peripheral resistance (Fig. 1) is accounted for by an effect on cardiac output.

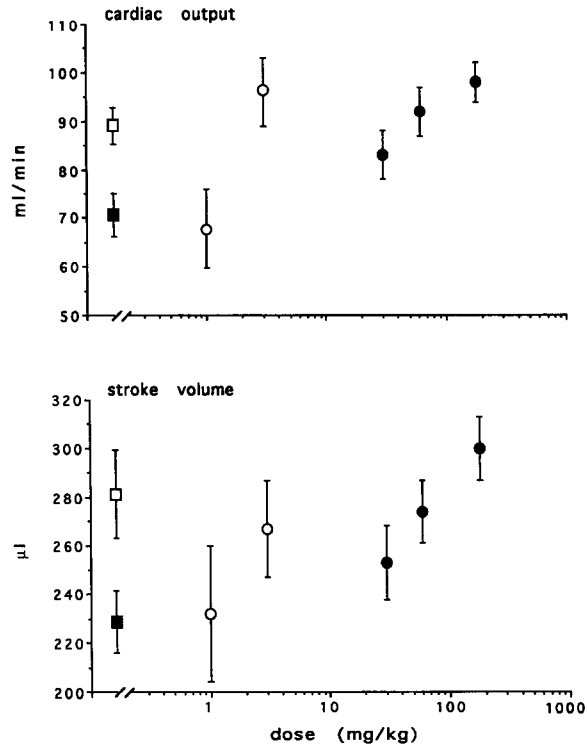

Fig. 2. Log dose-response effect of treatment with propionyl-l-carnitine (●) and enalapril (○) on peak cardiac output and stroke volume reached by pressure overloaded animals during increase in preload by i.v. infusion of physiological solution. The leftmost points indicate values reached by untreated sham (□) and clip (■) animals. Points represent the means ± S.E. from 7 to 14 animals.

The dose of 180 mg/kg propionyl-l-carnitine was also studied in sham rats. Results showed that it did not modify either basal or stimulated haemodynamics. Thus, for the sake of clarity data from this group are not included.

Enalapril treatment increased the peak cardiac output during acute volume loading (Fig. 1 and Fig. 2). This effect was dose-related ($P = 0.016$). Since in the 3 mg/kg group, heart rate increased progressively during saline infusion (from 309 ± 14 to 354 ± 13 at peak cardiac output, $P < 0.05$), stroke volume was not improved. In view of the effect of enalapril treatment on cardiac hypertrophy, data on peak cardiac output were analysed as a function of heart weight. Results showed no significant relation between cardiac output and left ventricle mass (not shown). Carotid blood pressure during volume loading rose to 111 ± 6 mmHg, a value

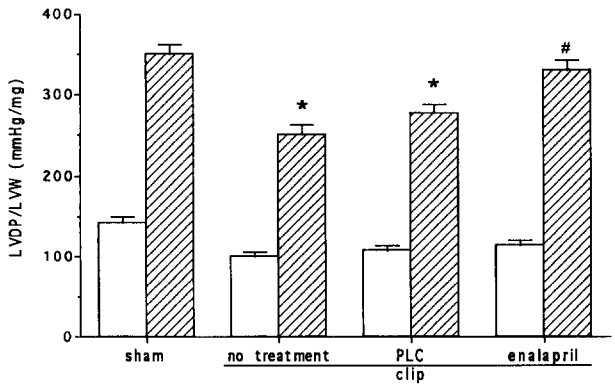

Fig. 3. Left ventricular developed pressure normalised to left ventricle weight before (open columns) and during (hatched columns) abrupt afterload increase induced by total aortic occlusion. Values are the means ± S.E. for (n) sham (9), untreated (14), 180 mg/kg propionyl-l-carnitine (12) and 3 mg/kg enalapril (10) treated pressure overloaded animals. In each group, values during aortic occlusion were significantly different than before ($P < 0.0001$, paired Student's t-test, not shown). $^{*}P < 0.005$ vs. sham, $^{\#}P < 0.005$ vs. clip.

significantly lower than those of both untreated and propionyl-l-carnitine-treated clip animals ($P < 0.05$). Total peripheral resistance values were comparable with those of sham animals (Fig. 1).

The results of abrupt aortic occlusion on left ventricular developed pressure are shown in Fig. 3 after normalization of the data by the left ventricle weight. The amount of pressure generated per unit of ventricular mass was significantly depressed in hypertrophied hearts of the clip group at maximum afterload.

This result was not modified by propionyl-l-carnitine treatment, even at the highest dose tested (Fig. 3). Conversely, enalapril treatment dose dependently improved the left ventricle pressure generating capacity during aortic occlusion (regression $P = 0.038$, not shown, and Fig. 3).

4. Discussion

This study demonstrates that a prolonged treatment with propionyl-l-carnitine was able to improve cardiac function in pressure-overloaded rats subjected to preload increase. The effect of propionyl-l-carnitine occurred in a dose-dependent fashion in the range 30–180 mg/kg.

In the pressure overload model employed here, under the experimental conditions used, basal performance was normal and only the imposition of additional load, preload or afterload, was able to reveal cardiac dysfunction. Assessment of the maximum left ventricle pressure generating capacity by total aortic occlusion showed that untreated pressure-overloaded rats have a diminished systolic performance. That is, although the maximum developed pressure was greater than in normal hearts, its normalization to the left ventricle weight clearly demonstrated that the pressure generated per unit of myocardium was lower, probably reflecting an increase in the non-myocyte compartment of the heart.

The acute volume loading allowed testing of the cardiac preload reserve. Both the normal and the hypertrophied hearts responded with an elevation of right atrial pressure and stroke volume. However, the Frank-Starling relationship of the hypertrophied hearts clearly indicated an impaired preload reserve (Fig. 1). These results are consistent with a decreased distensibility of the left ventricle wall, due to impaired relaxation, i.e. reduced Ca^{2+} reuptake, and to increased muscle stiffness, i.e. increased collagen content. Such changes are well known in pressure-overload concentric hypertrophy (Capasso et al., 1986; Jalil et al., 1989; Thiedemann et al., 1983).

Propionyl-l-carnitine treatment produced different effects on the two types of load stress. It improved cardiac output and stroke volume during the preload increase, allowing the hypertrophied hearts to perform comparably with control hearts. This effect occurred without modifying basal haemodynamics. Propionyl-l-carnitine did not increase the left ventricle pressure generating capacity. Since the increase in stroke volume may reflect an improvement in either ventricular filling or systolic performance, these results show that propionyl-l-carnitine acts on the former, increasing ventricular compliance. These data, together with the lack of any effect on the pump function of sham-operated animals, show that propionyl-l-carnitine does not behave as a conventional inotropic agent.

The aim of this work was to verify whether the effects induced by chronic propionyl-l-carnitine treatment on muscle mechanics in a pressure overload model (Micheletti et al., 1994) would bear any relevance to in vivo cardiac performance. In that study propionyl-l-carnitine normalized myosin composition and kinetic parameters. These effects may conceivably account for the results found here, since a faster ventricular relaxation should allow better chamber filling.

The lack of efficacy of propionyl-l-carnitine during aortic occlusion is in contrast with results obtained in the isolated working heart (Schönekess et al., 1994). A possible explanation is the substantially lesser degree of hypertrophy in the in vitro study, which may have resulted in a smaller functional impairment.

This study did not directly address the mechanism by which propionyl-l-carnitine improves cardiac function. Hypertrophic hearts display both carnitine depletion and depression of fatty acid oxidation (Allard et al., 1994; El-Alaoui Talibi et al., 1992; Reibel et al., 1983; Yang et al., 1992), but the relationship between these events is unclear. It has recently been shown that, unlike that found after acute administration (Pa-

ulson et al., 1986; Torielli et al., 1993; Yang et al., 1992), chronic propionyl-l-carnitine treatment did not increase fatty acid oxidation or ATP production from exogenous substrates, despite restoring carnitine content (Schönekess et al., 1994). Thus, even though the contribution of endogenous substrates to ATP production was not evaluated, these data point to an increase in cardiac efficiency (i.e., increase of the amount of cardiac work performed per unit of substrate used) of the hypertrophied heart following chronic propionyl-l-carnitine administration (Schönekess et al., 1994). It is plausible that this effect on cardiac efficiency and the reversal of the impairment in contraction and relaxation present from the beginning of cardiac hypertrophy may effectively stop or delay the development of heart failure.

The lower dose of enalapril tested, 1 mg/kg, failed to affect either cardiac function or the hypertrophic growth, despite its demonstrated ability to inhibit the angiotensin converting enzyme system, prolong survival after myocardial infarction (Sweet et al., 1987), and reduce left ventricular chamber expansion (Micheletti et al., 1993). Conversely, at a threefold greater dose, enalapril improved the cardiac function of pressure-overloaded rats both during an increase in preload and afterload, and reduced the hypertrophic growth. These functional and structural effects were unrelated, since cardiac function during preload increase was independent of ventricular mass.

The beneficial effect of angiotensin converting enzyme inhibitors in hypertensive disease has been attributed to the decrease both in preload and afterload (Pfeffer et al., 1982). In this study, a decrease in afterload was not apparently present under closed chest conditions, although the hypotensive effect of urethane (Maggi and Meli, 1986) may have masked differences present before anaesthesia. The decrease in blood pressure seen in this group after opening the chest might depend on antagonism of the angiotensin-mediated vasoconstrictive response. A treatment-induced reduction in preload may have also occurred and might be evidenced by the additional impairment in venous return due to thoracotomy. It may not be excluded that the improvement of cardiac output found in these animals was partly caused by the lower resistance.

A further effect of angiotensin converting enzyme inhibitors is local inhibition of angiotensin II-mediated effects on myocyte and collagen structure (Baker et al., 1990; Olivetti et al., 1993). However, the present data demonstrate that the functional benefit afforded by enalapril on cardiac function is independent of its effect on myocardial mass.

In conclusion, in the present study, in which pressure overload compromised the ability of the heart to meet the greater mechanical demand required by an increase in preload, propionyl-l-carnitine treatment improved cardiac performance probably by virtue of its ability to augment cardiac efficiency (Schönekess et al., 1994).

References

Allard, M.F., B.O. Schönekess, S.L. Henning, D.R. English and G.D. Lopaschuk, 1994, Contribution of oxidative metabolism and glycolysis to ATP production in the hypertrophied heart, Am. J. Physiol. 267, H742.

Baker, K.M., M.I. Chernin, S.K. Wixson and J.F. Aceto, 1990, Renin-angiotensin system involvement in pressure-overload cardiac hypertrophy in rats, Am. J. Physiol. 259, H324.

Bartels, G.L., W.J. Remme, M. Pillay, D.H.W. Schönfeld and D.A.C.M. Kruijssen, 1994, Effects of l-propionylcarnitine on ischemia-induced myocardial dysfunction in men with angina pectoris, Am. J. Cardiol. 74, 125.

Capasso, J.M., A. Malhotra, J. Scheuer and E.H. Sonnenblick, 1986, Myocardial biochemical, contractile, and electrical performance after imposition of hypertension in young and old rats, Circ. Res, 58, 445.

Caponnetto, S., C. Canale, M.A. Masperone, V. Terracchini, G. Valentini and C. Brunelli, 1994, Efficacy of l-propionylcarnitine treatment in patients with left ventricular dysfunction, Eur. Heart J. 15, 1267.

Corsico, N., A. Nardone, M.R. Lucreziotti, L.G. Spagnoli, D. Pesce, T. Aureli, M.E. Di Cocco, A. Miccheli, F. Conti and E. Arrigoni Martelli, 1993, Effect of propionyl-l-carnitine in a rat model of peripheral arteriopathy: a functional, histologic and NMR spectroscopic study, Cardiovasc. Drugs. Ther. 7, 241.

El Alaoui-Talibi and J. Moravec, 1993, Assessment of the cardiostimulant action of propionyl-l-carnitine on chronically volume-overloaded rat hearts, Cardiovasc. Drugs Ther. 7, 357.

El Alaoui-Talibi, Z., S. Landormy, A. Loireau and J. Moravec, 1992, Fatty acid oxidation and mechanical performance of volume overloaded rat hearts, Am. J. Physiol. 262, H1068.

Jalil, J.E., C.W. Doering, J.S. Janicki, R. Pick, S.G. Schroff and K.T. Weber, 1989, Fibrillar collagen and myocardial stiffness in the intact hypertrophied rat left ventricle, Circ. Res. 64, 1041.

Li, P., C. Park, R. Micheletti, B. Li, W. Cheng, E.H. Sonnenblick, P. Anversa and G. Bianchi, 1995, Myocyte performance during the evolution of myocardial infarction in rats: effects of propionyl-l-carnitine, Am. J. Physiol. 268, H1702.

Maggi C.A. and A. Meli, 1986, Suitability of urethane anesthesia for physiopharmacological investigations in various systems. Part 2: cardiovascular system, Experientia 42, 292.

Micheletti, R., E. Donato Di Paola, A. Schiavone, E. English, P. Benatti, J.M. Capasso, P. Anversa and G. Bianchi, 1993, Propionyl-l-carnitine limits chronic ventricular dilation after myocardial infarction in rats, Am. J. Physiol. 264, H1111.

Micheletti, R., G. Giacalone, M. Canepari, S. Salardi, G. Bianchi and C. Reggiani, 1994, Propionyl-l-carnitine prevents myocardial mechanical alterations due to pressure overload in rats, Am. J. Physiol. 266, H2190.

Olivetti, G., E. Cigola, C. Lagrasta, R. Ricci, F. Quaini, A. Monopoli and E. Ongini, 1993, Spirapril prevents left ventricular hypertrophy, decreases myocardial damage and promotes angiogenesis in spontaneously hypertensive rats, J. Cardiovasc. Pharmacol. 21, 362.

Paulson, D.J., J. Traxler, M. Schmidt, J. Noonan and A.L. Shug, 1986, Protection of the ischemic myocardium by L-propionylcarnitine: effects on the recovery of the cardiac output after ischemia and reperfusion, carnitine transport, and fatty acid oxidation, Cardiovasc. Res. 20, 536.

Pfeffer, J.M., M.A. Pfeffer, P. Fletcher, M.C. Fishbain and E. Braunwald, 1982, Favourable effects of therapy on cardiac performance in spontaneously hypertensive rats, Am. J. Physiol. 242, H776.

Reibel, D.K., C.E. Uboh and R.L. Kent, 1983, Altered coenzyme A and carnitine metabolism in pressure overload hypertrophied hearts, Am. J. Physiol. 244, H839.

Schönekess, B.O., M.F. Allard, R.M. Kozak, R.L. Barr and G.D. Lopaschuk, 1994 L-Propionylcarnitine feeding improves hypertrophied heart function, J. Mol. Cell. Cardiol. 26, CLXV.

Schönekess, B.O., M.F. Allard and G.D. Lopaschuk, 1995, Propionyl-l-carnitine improvement of hypertrophied heart function is accompanied by an increase in carbohydrate oxidation, Circ. Res. (in press).

Siliprandi, N., F. Di Lisa and R. Menabo', 1991, Propionyl-l-carnitine: biochemical significance and possible role in cardiac metabolism, Cardiovasc. Drugs Ther. 5, 45.

Sweet, C.S., S.E. Emmert, I.I. Stabilito and L.G.T. Ribeiro, 1987, Increased survival in rats with congestive heart failure treated with enalapril, Eur. J. Pharmacol. 10, 636.

Tassani, V., F. Cattapan, L. Magnanimi and A. Peschechera, 1994, Anaplerotic effect of propionyl-l-carnitine in rat heart mitochondria, Biochem. Biophys. Res. Comm. 199, 949.

Thiedemann, K.U., C. Holubarsch, I. Medugorac and R. Jacob, 1983, Connective tissue content and myocardial stiffness in pressure overload hypertrophy: a combined study of morphologic, morphometric, biochemical and mechanical parameters, Basic Res. Cardiol. 78, 140.

Torielli, L., F. Conti, E. Cinato, E. Ceppi, P. Anversa, G. Bianchi and P. Ferrari, 1995, Alterations in energy metabolim of hypertrophied rat cardiomyocytes: influence of propionyl-l-carnitine, J. Cardiovasc. Pharmacol. (in press).

Weinberg, E.O., F.J. Schoen, D. George and B.H. Lorell, 1993, ACE inhibition improves survival and modifies the transition to failure in aortic-banded rats with persistent pressure overload, Circulation 88, I8.

Yang, X.P., M. Samaja, E. English, P. Benatti, M. Tarantola, G. Cardace, R. Motterlini, R. Micheletti and G. Bianchi, 1992, Hemodynamic and metabolic activities of propionyl-l-carnitine in rats with pressure-overload cardiac hypertrophy, J. Cardiovasc. Pharmacol. 20, 88.