# Effects of L-Propionylcarnitine on Ischemia-Induced Myocardial Dysfunction in Men with Angina Pectoris

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**To identify the effect of L-propionylcarnitine (LPC) on ischemia, 31 fasting, untreated male patients with left coronary artery disease were studied during 2 identical pacing stress tests 45 minutes before (atrial pacing test I [APST I]) and 15 minutes after (APST II) administration of 15 mg/kg of LPC or placebo. Hemodynamic, metabolic, and nuclear angiographic variables were studied before, during, and for 10 minutes after pacing. After LPC administration, arterial total carnitine levels increased from 47 ± 1.7 μmol/liter (control) to 730 ± 30 μmol/liter. Hemodynamic and metabolic variables were comparable in LPC and placebo during APST I, and reproducible in placebo during both tests. Although LPC did not affect myocardial oxygen demand and supply, it diminished myocardial ischemia, indicated by a significant 12% and 50% reduction in ST-segment depression and left ventricular end-diastolic pressure, respectively, during APST II. Moreover, during APST II, left ventricular ejection fraction increased by 18% ($p < 0.05$ vs APST I). Furthermore, LPC improved recovery of myocardial function after pacing, with a reduction in the time to peak filling and a 21% increase in both peak ejection and filling rates 10 minutes after pacing (all $p < 0.05$). Thus, LPC prevents ischemia-induced ventricular dysfunction, not by affecting the myocardial oxygen supply-demand ratio but as a result of its intrinsic metabolic actions, increasing pyruvate dehydrogenase activity and flux through the citric acid cycle. Because it is well tolerated, it may be a valuable alternative or addition to available anti-ischemic therapy.**

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Because available anti-ischemic agents are often inadequate due to incomplete efficacy or adverse effects, there is a need for alternative pharmacologic strategies (e.g., metabolic anti-ischemic therapy). L-carnitine mediates mitochondrial fatty acid transport and regulates mitochondrial high-energy phosphate exchange through the activity of adenine nucleotide translocase.[1,2] Moreover, it stimulates pyruvate dehydrogenase and improves the flux of pyruvate into the citric acid cycle.[3] As the heart is unable to synthesize L-carnitine, it is critically dependent on external supply.[4,5] During ischemia, total and free myocardial carnitine levels decrease.[6,7] In addition, acyl coenzyme A (CoA) accumulates and inhibits adenine nucleotide translocase and pyruvate dehydrogenase activity. Administration of L-carnitine may reverse this inhibition.[1] In both animals and humans, anti-ischemic effects of L-carnitine have been reported.[8–11] L-propionylcarnitine (LPC), a natural derivative of L-carnitine, may be more effective in this respect, because it is more rapidly accessible to the cardiocyte[12,13] and may increase the citric acid flux through newly formed propionyl-CoA.[14] Indeed, animal models of ischemia-reperfusion indicate a protective effect of intravenous LPC.[15,16] Because no human data are available, the present study evaluated the anti-ischemic effects of intravenous LPC in patients with coronary artery disease.

## METHODS

**Patients:** After approval of the institutional ethical review board and informed consent, 31 normotensive male patients aged 46 to 73 years (mean 57) with angina pectoris and objective signs of exercise-induced ischemia were evaluated. Twenty patients had a documented myocardial infarction. Patients with unstable angina, arterial hypertension (systolic pressure >220 mm Hg, diastolic pressure >100 mm Hg), symptoms or signs of congestive heart failure, conduction abnormalities, valvular heart disease, diabetes mellitus, and renal or hepatic dysfunction were excluded. Previous myocardial infarctions had to be at least 1 month old. All cardiac medication was withheld 24 to 72 hours before the investigation. Only short-acting nitroglycerin was allowed until 6 hours before the study. None of the patients received digitalis. To participate, patients had to have a diameter stenosis of ≥70% in either the left anterior descending artery, a diagonal branch, the proximal part of the left circumflex artery, or a proximal marginal branch. Nine patients had 1-vessel, 11 patients 2-vessel, and 11 patients 3-vessel disease.

**TABLE I** Baseline Characteristics of Patients

| | L-Propionylcarnitine | Placebo |
|---|---|---|
| Number of patients | 15 | 16 |
| Age (years) | 59 ± 2 | 58 ± 2 |
| Previous myocardial infarction | 13* | 7 |
| Anterior | 6 | 3 |
| Inferior | 8 | 4 |
| Number of coronary arteries narrowed >70% in diameter | | |
| 1 | 6 | 3 |
| 2 | 3 | 8 |
| 3 | 6 | 5 |
| Left ventricle | | |
| End-diastolic volume (ml/m²) | 73 ± 6 | 62 ± 5 |
| Ejection fraction (%) | 43 ± 4 | 50 ± 3 |

*p <0.05 L-propionylcarnitine versus placebo.
Data are mean ± SEM.

**Instrumentation:** Studies were conducted in the morning, without premedication and with the patient fasting. First, left and right coronary angiography was performed, using the Seldinger technique. If patients met the inclusion criteria, a no. 7Fr thermodilution flow and pacing catheter (Wilton Webster Laboratories) was advanced into the midportion of the coronary sinus through a brachial vein so that its position was stable and blood could be drawn easily. The absence of atrial reflux was confirmed by bolus injections of saline solution at room temperature in the right atrium. Next, a no. 7Fr triple-lumen thermodilution catheter was positioned in a pulmonary artery through the right femoral vein and a no. 8Fr Sentron pigtail microtip manometer catheter advanced into the left ventricle through a no. 9Fr Desilet introducer system in the right femoral artery. The side arm of the latter was used to monitor arterial pressures. The position of the catheters was recorded on video and checked throughout the study.

**Hemodynamic and electrocardiographic measurements:** All fluid-filled catheters were calibrated using a zero reference level set at midchest. Pressures in the right atrium and in the femoral and pulmonary arteries were measured using Bentley transducers (Baxter-Bentley, Uden, The Netherlands). All pressures were recorded on paper at different paper speeds (i.e., at 10, 25, and 100 mm/s) using a Nihon Kohden cath lab system. In addition, pressure-derived contractility and relaxation indexes were determined on-line by a Mennen cath lab computer system. In a beat-to-beat analysis, this system averages 15 to 20 consecutive beats to level out respiratory variations. Coronary sinus blood flow was determined during a continuous 30-second infusion of 50 ml of 5% glucose at room temperature.[17] Electrocardiographic leads I, II, and $V_5$ were continuously monitored. The ST-segment level was assessed with a calibrated magnifying lens in 5 consecutive beats 0.08 second after the J point at a paper speed of 100 mm/s.

**Metabolic measurements:** Blood sampling for metabolic determinations was performed simultaneously from the left ventricle and the coronary sinus. Oxygen saturation was determined with an OSM-80 oximeter (Waters Associates). For lactate, exactly 1 ml was sampled in 2 ml of ice cold 0.6 M perchloric acid, and analyzed as previously reported.[18] Blood samples (1 ml) for hypoxanthine analysis were collected in precooled heparinized tubes containing 0.5 ml of 40 μM of dipyridamole and 0.5 ml of 20 μM of erythro-9-(2-hydroxy-3-nonyl) adenine. Hypoxanthine was assayed by dual-column high-pressure liquid chromatography as reported.[18] The standard deviation is 0.2 μM. For the analysis of free and total L-carnitine, 2 ml of arterial blood was collected in precooled tubes containing 500 IU of heparin. Free L-carnitine was determined by radioenzymatic assay (SD = 0.8 μmol/liter) and total L-carnitine, after hydrolysis by 0.1 M potassium hydroxide and neutralization with 0.5 M N-[2-hydroxyethyl]piperazine-N′-[2-ethanesulfonic acid], was determined radioenzymatically (SD = 1.0 μmol/liter).[19]

**Scintigraphic measurements:** After in vivo labeling with 1,000 MBq of technetium-99m, radionuclide angiography was performed in a 35° to 40° left anterior oblique projection with an approximate 10° cranial tilt using a mobile LEM gamma camera (Siemens) equipped with a low-energy, all-purpose collimator, and connected on-line with a mobile MCS/560 nuclear computer system (General Electric). A 20% window was set around the 140 KeV gamma peak and data were collected in a 64 × 64 matrix using a 1.5× zoom. Framing intervals were calculated to produce 16 frames/cycle. Cardiac cycles, with a cycle length that differed >10% from the average cycle length recorded just before acquisition, were automatically excluded from analysis. Imaging lasted 8 minutes at baseline and 4 minutes during pacing and after pacing. Data analysis was performed with a Sophy P computer (Sopha Medical) using the methods described by Magorien et al.[20] The following variables were determined: left ventricular ejection fraction (%), wall motion changes (≥5% points change in 9 sectorial ejection fractions), time to peak filling and ejection rate (ms), and peak ejection and filling rate ($sec^{-1}$).

**Drug administration:** Patients received either LPC (15 mg/kg) or its vehicle (15 mg/kg mannitol and 19.5 mg/kg sodium anhydrous in 0.25 mg/kg distilled water) over a 5-minute period in a double-blind, randomized fashion.

**Study protocol:** After instrumentation, a stabilization period of ≥20 minutes was allowed to achieve a minimal interval of 45 minutes between coronary angiography and the study. Multiple control determinations of all hemodynamic variables were then performed to ensure stable baseline values. Next, the first atrial pacing stress test (APST I) was performed, with increments in heart rate of 10 beats/2 minutes, until angina, atrioventricular block, or a maximal heart rate of 170 beats/min was reached. Forty-five minutes after APST I, after reassessing hemodynamic, scintigraphic, and metabolic variables, patients received either LPC or vehicle. Twenty minutes after the onset of drug infusion, a second atrial pacing stress test (APST II), identical to APST I, was performed. During both tests, hemodynamic variables, lactate, and oxygen were determined at baseline, maximal pacing, and at 15 seconds, 1, and 10 minutes after pacing. Hypoxanthine levels were determined at control, maximal pacing, and 1 minute after pacing. Arterial carnitine levels were determined before

and 5, 15, and 45 minutes after the start of the drug infusion.

**Data analysis:** Data are presented as mean ± SEM. The statistical analysis consisted of a *t* test for paired observations and an analysis of variance to differentiate between group differences at the respective time points. A 2-tailed p value <0.05 was considered a significant difference.

## RESULTS

LPC was administered to 15 patients and placebo to 16 patients. Baseline clinical and demographic data are listed in Table I. Both groups were comparable as to age, sex, number of coronary lesions, and left ventricular function. Old myocardial infarctions were present in 13 patients in the LPC group versus 7 in the placebo group (p <0.05).

**Hemodynamic and electrocardiographic changes during pacing:** Baseline systemic and coronary hemodynamic variables were comparable in both groups (Tables II and III). In the placebo group, APST I resulted in myocardial ischemia indicated by ST-segment depression of −0.15 ± 0.03 mV, and an increase in left ventricular end-diastolic pressure from 14 ± 1 (baseline) to 21 ± 2 mm Hg immediately after pacing (Figure 1). All parameters returned to baseline values between 5 and 10 minutes after pacing. During APST II, baseline values and changes in hemodynamic and electrocardiographic parameters were similar to those observed during APST I in placebo-treated patients.

In the LPC group, changes during and after APST I were similar to those in the placebo patients, except for cardiac index, which was still significantly reduced in the LPC group 30 minutes after pacing. Hemodynamic changes were comparable during both pacing tests. In contrast to placebo, LPC reduced left ventricular end-diastolic pressure after pacing by 50% (Figure 1) and resulted in a moderate but significant reduction in ST-segment depression during APST II, whereas the decrease in cardiac index after APST I was prevented after APST II (all p <0.05, APST II vs I).

**Metabolic changes:** At baseline, myocardial lactate and hypoxanthine extraction values were comparable in both groups (Table III). In the placebo group, a significant but reproducible cardiac release of both metabolites was observed. During APST I, similar changes occurred in the LPC group. At the start of APST II, 15 minutes after LPC administration, myocardial lactate extraction had increased by 24%. Whereas myocardial lactate production was comparable during both tests in LPC, the change from hypoxanthine uptake to release was significantly less during APST II.

**Scintigraphic determinations:** At baseline, all variables were comparable in both groups (Table IV). Also, changes in peak ejection and filling rate during APST I were comparable in both groups, and during both tests in the placebo group. In the latter, left ventricular ejection fraction did not change throughout the study. In contrast, it increased by 18% during APST II after LPC (p <0.05), together with a significant wall motion score improvement in all but 2 patients. Moreover, and in contrast to the placebo group, LPC improved recovery of myocardial function after pacing with a 21% increase in peak ejection and peak filling rate and a reduction in time to peak filling (−42 ms) 10 minutes after pacing compared with results after APST I (p <0.05).

**Carnitine plasma levels:** The baseline plasma levels of free and total carnitine were similar in placebo (35 ± 1.7 and 46 ± 1.6 μmol/liter, respectively) and LPC (36 ± 1.5 and 47 ± 1.7 μmol/liter, respectively) groups. In the placebo group, arterial levels of total and free carnitine remained unaltered throughout the study. In the treated group, the plasma level of total carnitine increased 15-fold immediately after the infusion of 15 mg/kg of LPC, but subsequently decreased to 5 times the baseline level 10 minutes after pacing, approximately 40 minutes after drug administration (Figure 2). Free carnitine levels increased four- to fivefold, and decreased to 92 ± 6 μmol/liter, 2.5 times baseline levels at the end of the study.

**Adverse effects:** None of the patients experienced any adverse effects.

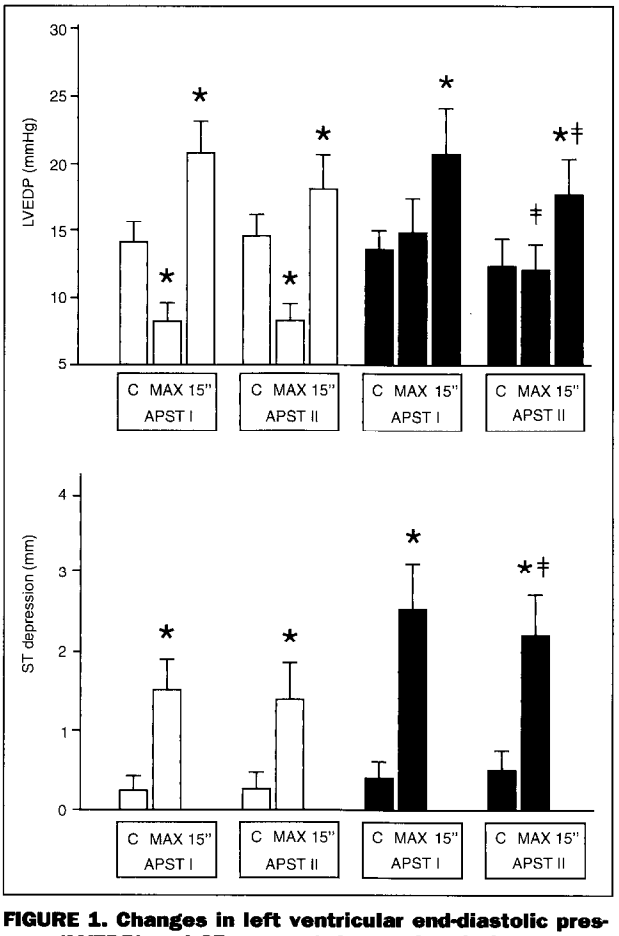


**FIGURE 1. Changes in left ventricular end-diastolic pressure (LVEDP) and ST-segment depression during the atrial pacing stress test before (APST I) and after (APST II) placebo *(open bars)* or L-propionylcarnitine *(black bars)* administration. L-propionylcarnitine reduces myocardial ischemia as seen by a 45% reduction in left ventricular end-diastolic pressure immediately after pacing and a 10% reduction in ST-segment depression during pacing. Values are expressed as mean ± SEM. *p <0.05 versus control; ‡p <0.05, changes during APST I versus changes during APST II. C = control; M = maximal pacing; 15" = 15 seconds after pacing.**

**TABLE II** Systemic Hemodynamic Changes During Both Pacing Tests

| | Placebo (n=16) / LPC (n=15) | APST I | | Postpacing | | Control | APST II | | Postpacing | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | Maximal | 15 Sec. | 10 Min. | Drug Infusion | Control | Maximal | 15 Sec. | 10 Min. |
| HR ($min^{-1}$) | Placebo | 72 ± 3 | 148 ± 5* | 71 ± 4 | 75 ± 4 | 73 ± 4 | 74 ± 3 | 148 ± 4* | 78 ± 6 | 79 ± 3 |
| | LPC | 73 ± 2 | 138 ± 5* | 79 ± 3* | 75 ± 2 | 74 ± 2 | 77 ± 2† | 138 ± 5* | 82 ± 3* | 80 ± 3 |
| LVSP (mm Hg) | Placebo | 148 ± 5 | 147 ± 3 | 152 ± 5 | 149 ± 5 | 149 ± 4 | 147 ± 5 | 144 ± 5 | 151 ± 7 | 149 ± 6 |
| | LPC | 148 ± 7 | 141 ± 6 | 148 ± 7 | 147 ± 6 | 147 ± 5 | 149 ± 6 | 140 ± 5* | 147 ± 6 | 150 ± 6 |
| dP/dt pos. (mm $Hg/s^{-1}$) | Placebo | 1,701 ± 108 | 2,342 ± 165* | | 1,682 ± 122 | 1,699 ± 103 | 1,637 ± 92 | 2,345 ± 166* | | 1,730 ± 108 |
| | LPC | 1,508 ± 71 | 1,887 ± 113* | | 1,466 ± 71 | 1,480 ± 66 | 1,484 ± 71 | 1,894 ± 107* | | 1,521 ± 62 |
| Vmax ($s^{-1}$) | Placebo | 50 ± 3 | 63 ± 3* | | 48 ± 3 | 49 ± 2† | 48 ± 2† | 63 ± 3* | | 49 ± 2 |
| | LPC | 44 ± 2 | 55 ± 3* | | 42 ± 1 | 42 ± 2 | 43 ± 2 | 56 ± 3* | | 42 ± 2 |
| $Vce_{40}$ ($s^{-1}$) | Placebo | 34 ± 2 | 45 ± 2* | | 33 ± 2 | 33 ± 2 | 32 ± 2† | 45 ± 2* | | 34 ± 2 |
| | LPC | 30 ± 1 | 39 ± 2* | | 29 ± 1 | 29 ± 1 | 29 ± 1 | 39 ± 2* | | 29 ± 1 |
| $Tau_1$ (ms) | Placebo | 48 ± 3 | 41 ± 2* | | 49 ± 3 | 50 ± 3† | 50 ± 3 | 42 ± 2* | | 49 ± 2 |
| | LPC | 51 ± 2 | 44 ± 3* | | 52 ± 2 | 53 ± 3† | 51 ± 3 | 45 ± 3† | | 52 ± 3 |
| MAP (mm Hg) | Placebo | 100 ± 2 | 116 ± 3* | 102 ± 3 | 103 ± 3 | 104 ± 3 | 105 ± 3 | 115 ± 4* | 102 ± 3 | 107 ± 4 |
| | LPC | 104 ± 5 | 111 ± 6* | 108 ± 7 | 104 ± 6 | 107 ± 5 | 108 ± 6 | 115 ± 6* | 112 ± 5 | 111 ± 6 |
| SVR (dynes s $cm^{-5}$) | Placebo | 1,369 ± 77 | | | 1,432 ± 105 | 1,478 ± 84 | 1,463 ± 99 | | | 1,531 ± 106 |
| | LPC | 1,430 ± 115 | | | 1,465 ± 112 | 1,639 ± 127† | 1,583 ± 129† | | | 1,581 ± 102 |
| CI ($L \cdot min^{-1} \cdot m^{-2}$) | Placebo | 2.9 ± 0.1 | | | 2.8 ± 0.1 | 2.8 ± 0.1 | 2.8 ± 0.1 | | | 2.8 ± 0.1 |
| | LPC | 2.9 ± 0.1 | | | 2.6 ± 0.1* | 2.6 ± 0.1† | 2.7 ± 0.1 | | | 2.7 ± 0.2‡ |

*p <0.05 versus control; †p <0.05 versus control APST I; ‡p <0.05, change during APST I versus change during APST II.
Data are mean ± SEM.
APST = atrial pacing stress test; CI = cardiac index; dP/dt pos. = maximal dP/dt; HR = heart rate; LVSP = left ventricular peak systolic pressure; MAP = mean arterial pressure; SVR = systemic vascular resistance; $Tau_1$ = time constant of relaxation; Vmax, $Vce_{40}$ = velocity indexes.

**TABLE III** Coronary Hemodynamic and Myocardial Energetic and Metabolic Parameters

| | Placebo (n=16) / LPC (n=15) | APST I | | Postpacing | | Control | APST II | | Postpacing | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | Maximal | 15 Sec. | 10 Min. | Drug Infusion | Control | Maximal | 15 Sec. | 10 Min. |
| DP | Placebo | 11 ± 1 | 22 ± 1* | 11 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 1 | 21 ± 1* | 12 ± 1 | 12 ± 1 |
| (mm Hg/min) | LPC | 11 ± 1 | 20 ± 1* | 12 ± 1 | 11 ± 1 | 11 ± 1 | 11 ± 1 | 19 ± 1* | 12 ± 1 | 12 ± 1 |
| CSBF | Placebo | 144 ± 16 | 214 ± 20* | | 128 ± 9 | 120 ± 9 | 127 ± 13 | 200 ± 15* | | 127 ± 9 |
| ($ml \cdot min^{-1}$) | LPC | 114 ± 13 | 155 ± 16* | | 115 ± 16 | 106 ± 14 | 112 ± 15 | 161 ± 15* | | 115 ± 17 |
| CVR | Placebo | 0.77 ± 0.07 | 0.64 ± 0.07* | | 0.86 ± 0.07 | 0.95 ± 0.09† | 0.97 ± 0.11† | 0.62 ± 0.05* | | 0.93 ± 0.08 |
| (mm Hg/ml/min) | LPC | 1.06 ± 0.14 | 0.81 ± 0.08* | | 1.13 ± 0.17 | 1.24 ± 0.17† | 1.16 ± 0.13 | 0.79 ± 0.07* | | 1.15 ± 0.11 |
| $\Delta A\text{-}CSO_2$ (ml) | Placebo | 13 ± 1 | 14 ± 1 | | 14 ± 1 | 14 ± 1 | 13 ± 1 | 14 ± 1 | | 14 ± 1 |
| | LPC | 14 ± 1 | 14 ± 1 | | 14 ± 1 | 14 ± 1 | 13 ± 1 | 14 ± 1 | | 14 ± 1 |
| $mVO_2$ (ml/min) | Placebo | 20 ± 3 | 29 ± 4* | | 17 ± 2 | 17 ± 2 | 16 ± 2 | 28 ± 3* | | 18 ± 2 |
| | LPC | 17 ± 2 | 22 ± 2* | | 15 ± 2 | 15 ± 2 | 16 ± 2 | 23 ± 2* | | 16 ± 3 |
| Lactate (A-V) | Placebo | 0.16 ± 0.02 | 0.05 ± 0.03* | −0.13 ± 0.09* | 0.16 ± 0.03 | 0.18 ± 0.05 | 0.24 ± 0.05† | 0.04 ± 0.05*‡ | −0.14 ± 0.13* | 0.12 ± 0.02* |
| (mmol/L) | LPC | 0.19 ± 0.04 | 0.00 ± 0.08* | −0.22 ± 0.13* | 0.20 ± 0.05 | 0.16 ± 0.04 | 0.23 ± 0.04† | −0.01 ± 0.08* | −0.09 ± 0.12* | 0.13 ± 0.02* |
| Lactate | Placebo | 22 ± 3 | 8 ± 4 | −20 ± 15* | 20 ± 4 | 20 ± 5 | 28 ± 3 | 4 ± 5*‡ | −21 ± 16* | 16 ± 3* |
| extraction (%) | LPC | 25 ± 3 | −1 ± 10 | −33 ± 17* | 25 ± 4 | 21 ± 3 | 31 ± 3† | −5 ± 11*‡ | −21 ± 17* | 20 ± 4* |
| Hypoxanthine | Placebo | 2.4 ± 0.8 | 0.1 ± 0.3* | −2.8 ± 1.4* | | | 1.0 ± 0.5† | 0.0 ± 0.3* | −2.6 ± 0.8* | |
| (A-V) (μmol/L) | LPC | 2.5 ± 0.6 | 1.2 ± 0.9* | −0.5 ± 1.1* | | | 0.8 ± 0.3† | 0.3 ± 0.6 | −0.5 ± 1.2‡ | |

*p <0.05 versus control; †p <0.05 versus control APST I; ‡p <0.05, change during APST I versus change during APST II.
Data are mean ± SEM.
APST = atrial pacing stress test; $\Delta A\text{-}CSO_2$ = arterial and coronary venous difference in oxygen content; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; DP = double product (heart rate • left ventricular systolic pressure $\cdot 10^{-3}$); Hypoxanthine (A-V) = arterial and coronary venous difference in hypoxanthine content; Lactate (A-V) = arterial and coronary venous difference in lactate content; Lactate extraction = (arterial lactate − coronary venous lactate)/arterial lactate • 100%; $mVO_2$ = myocardial oxygen consumption.

**TABLE IV** Scintigraphic Changes During Both Pacing Tests

| | Placebo (n=16) | APST I | | Postpacing | Control | APST II | | Postpacing |
|---|---|---|---|---|---|---|---|---|
| | LPC (n=15) | Control | Maximal | (10 min) | Drug Infusion | Control | Maximal | (10 min) |
| GEF | Placebo | 50 ± 3 | 48 ± 5 | 49 ± 4 | 49 ± 4 | 47 ± 4 | 50 ± 3 | 48 ± 4 |
| | LPC | 43 ± 4 | 43 ± 4 | 39 ± 3 | 39 ± 3† | 38 ± 4 | 45 ± 4‡ | 39 ± 4 |
| TPE | Placebo | 123 ± 12 | 109 ± 10 | 128 ± 16 | 139 ± 15 | 131 ± 12 | 111 ± 18* | 136 ± 16 |
| | LPC | 157 ± 23 | 111 ± 11 | 139 ± 15 | 138 ± 17 | 150 ± 15 | 114 ± 13 | 167 ± 12 |
| PER | Placebo | 2.47 ± 0.22 | 4.04 ± 0.43* | 2.46 ± 0.29 | 2.33 ± 0.23 | 2.27 ± 0.25 | 4.20 ± 0.31* | 2.58 ± 0.30 |
| | LPC | 2.05 ± 0.18 | 3.64 ± 0.39* | 1.85 ± 0.13 | 1.84 ± 0.14 | 1.83 ± 0.18 | 3.88 ± 0.38* | 2.19 ± 0.20*‡ |
| TPF | Placebo | 498 ± 12 | 286 ± 16* | 509 ± 14 | 519 ± 13† | 503 ± 11 | 308 ± 13* | 500 ± 15 |
| | LPC | 504 ± 12 | 330 ± 15* | 522 ± 13 | 528 ± 13† | 521 ± 14 | 313 ± 14* | 497 ± 16*‡ |
| PFR | Placebo | 2.22 ± 0.21 | 3.49 ± 0.43* | 2.14 ± 0.19 | 2.05 ± 0.17 | 2.00 ± 0.22 | 4.05 ± 0.43* | 2.13 ± 0.20 |
| | LPC | 1.55 ± 0.16 | 3.10 ± 0.46* | 1.44 ± 0.14 | 1.30 ± 0.15† | 1.26 ± 0.13† | 2.87 ± 0.45* | 1.53 ± 0.15*‡ |

*p <0.05 versus control; †p <0.05 versus control APST I; ‡p <0.05, change during APST I versus change during APST II.
Data are mean ± SEM.
APST = atrial pacing stress test; GEF = left ventricular ejection fraction (%); PER = peak ejection rate ($s^{-1}$); PFR = peak filling rate ($s^{-1}$); TPE = time to peak ejection (ms); TPF = time to peak filling (ms); other abbreviations as in Table I.

## DISCUSSION

In the present study, the potential of LPC to reduce myocardial ischemia following intravenous administration was evaluated in a double-blind, placebo-controlled fashion in patients with coronary artery disease. Whereas the anti-ischemic effects of LPC were already present during pacing, they were most pronounced in the immediate and late postpacing period. Immediately after pacing with LPC, the increase in left ventricular filling pressures was significantly reduced, indicating better preservation of compliance, as compared with results after APST I. In addition, LPC improved scintigraphic measures of contractility and relaxation and prevented the reduction in cardiac output observed after the first untreated pacing test.

So far, several animal studies have reported the ability of LPC to improve mechanical recovery after myocardial ischemia.[13,15,16,21,22] The present study indicates that LPC may have similar beneficial effects during acute myocardial ischemia and the early recovery phase in humans.

**Anti-ischemic properties of L-propionylcarnitine—underlying mechanisms:** In the present study, LPC did not affect myocardial ischemia by modulating the myocardial oxygen supply-demand ratio. In anesthetized dogs, 200 mg/kg of intravenous LPC results in coronary and peripheral vasodilation.[23] Moreover, in pigs, 50 mg/kg of LPC improves myocardial blood flow during reperfusion after 60 minutes of ischemia.[16] In a previous study, we were unable to observe any acute vasodilating effects of 15 mg/kg of LPC.[24] This difference in results between animal and human data may relate to different dosages, a different model of ischemia and reperfusion, and the inability to measure regional coronary flow changes in our study. However, the complete absence of any coronary vasodilating effect of LPC in our study and the absence of changes in myocardial oxygen consumption make a drug-induced improvement in myocardial oxygen supply unlikely. Also, LPC did not affect the rate-pressure product or myocardial contractility during pacing, which indicates that the compound does not interfere with myocardial oxygen demand. Moreover, an increase in citric acid cycle activity should be accompanied by an increase in myocardial oxygen consumption. Although this may be true in the regional ischemic area, an overall metabolic effect is less likely.

**Effects of L-propionylcarnitine during the early recovery phase:** Taken together, the anti-ischemic effects of LPC were moderate during pacing-induced stress, but, in contrast, more prominent during the recovery phase after pacing. As such, our findings agree with observations from animal ischemia-reperfusion studies.[13,15] In the present study, both systolic and diastolic cardiac function and cardiac output were significantly enhanced during the first 10 minutes of recovery after pacing following LPC. This improvement was not mediated by changes in pre- and afterload or heart rate. More likely, enhanced metabolic recovery and increased myocardial energy stores are involved. In animal ischemia-reperfusion experiments, LPC increases high-energy phosphate concentrations and stimulates fatty acid oxidation during the reperfusion period.[25,26] Moreover, through modulation of the activity of adenine nucleotide translocase, carnitine is likely to promote adenosine triphosphate transfer from the mitochondrium to the contractile protein site. Finally, the anaplerotic mechanism

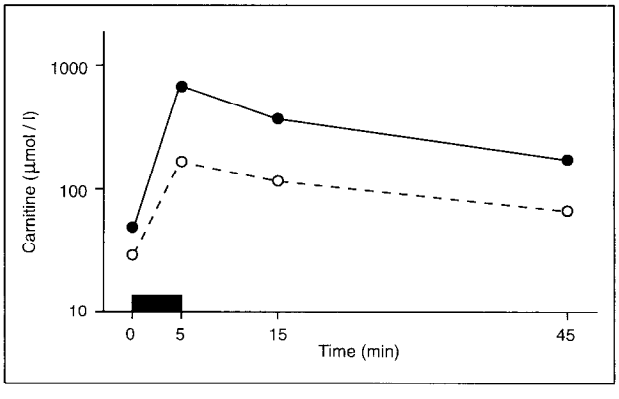


**FIGURE 2. Arterial levels of total *(closed circles)* and free *(open circles)* carnitine before and after infusion of 15 mg/kg of L-propionylcarnitine *(black bar)*. Both total and free carnitine plasma levels increased quickly after intravenous administration after which the total carnitine plasma level decreased more rapidly than the free carnitine plasma level. Values are expressed as mean ± SEM.**

of LPC whereby propionyl-CoA is converted to succinyl-CoA, subsequently improving the citric acid flux, may be more effective during reperfusion and recovery, when oxygen is again available and the electron transport chain is free to run.

**Clinical implications:** Our study indicates that LPC acutely reduces myocardial ischemia and improves cardiac function in the recovery period following a short period of ischemia, a modulation that is most likely mediated through its metabolic properties. This alternative mode of action and the absence of any untoward effects suggest a role for LPC in modulating the functional consequences of acute myocardial ischemia and reperfusion.


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