# Carnitine-Induced Effects on Cardiac and Peripheral Hemodynamics

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CARNITINE ($\beta$ - hydroxy - $\gamma$ - trimethyl-aminobutyric acid) is a naturally occurring amino acid found in all living tissue, with the highest endogenous levels present in the adrenal glands and in skeletal and cardiac muscle.[1,2] Previous reports have demonstrated a variety of beneficial cardiac effects of exogenous carnitine in the experimental animal heart and in man: a protective effect against palytoxin- and diphtheria-induced myocardial toxicity in the rat,[3,4] cardiac dysrhythmias[5] and certain myocardial ischemic changes in the dog,[6,7] and an improved stress tolerance of the ischemic myocardium in man.[8] This study was undertaken to determine, in the normal dog, the dose-related effects of carnitine infusion on cardiac, pulmonary, and systemic hemodynamics.

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## Material and Methods

Experiments were performed in 22 healthy, mongrel dogs of both sexes, ranging in weight from 12 to 27 kg. The animals were weighed, and anesthesia was rapidly induced with a 2% solution of thiopental sodium followed by maintenance of stage III anesthesia using a warmed solution of alpha-chloralose. Chloralose anesthesia has been shown to have only minimal and transient effects on cardiovascular dynamics.[9] Supplementary doses of chloralose were given to maintain a relatively uniform state of anesthesia during the thoracotomy and instrumentation; however, no anesthetic was given after control measurements were made. Respiration was controlled by a Harvard volume respirator regulated to maintain a blood pH of $7.50 \pm 0.05$. The pump was connected to a tracheotomy tube, and steady supplemental oxygen was administered to maintain arterial blood saturation above 95 per cent throughout the experiment. The heart was exposed by a median sternotomy, pericardiotomy was performed, and a pericardial cradle was created to support the exposed heart. If the animal was judged to be volume depleted (as evidenced by a low right atrial pressure), saline was infused to correct



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the deficit (50 to 150 ml) before the experiment.

All cardiovascular pressures were measured at the midpoint of the right atrium. Left ventricular pressure was measured through a short (4 in.) 14-T-gauge, semirigid Teflon needle (Becton, Dickinson and Co., Rutherford, N.J.) inserted into the ventricular apex and connected directly to a Statham P23 Db pressure transducer without intervening tubing. This system has a frequency response linear beyond 75 Hz. Systemic and pulmonary artery pressures were measured from Teflon catheters inserted into the carotid and pulmonary arteries. An electromagnetic flowmeter cuff probe was placed around the proximal ascending aorta, and blood flow was measured with a dual-channel gated sine-wave flowmeter (Biotronex Laboratories, Silver Springs, Md.). Left ventricular contractile force was measured by an isometric strain gauge of the Walton-Brodie type sutured to the myocardium parallel to outer wall fibers. In five dogs, left circumflex blood flow was measured. A short segment of the artery near its origin was dissected free of adjacent tissue. A flow transducer of appropriate size to ensure a snug fit was applied to the vessel and simultaneous mean and pulsatile coronary blood flow was recorded. Zero reference was obtained by mechanical occlusion of the artery with a silk snare around the artery just distal to the flow transducer.

*dl*-Carnitine HCl was infused intravenously at constant rates ranging from 10 to 70 mg/kg per minute. In the initial experiments, measurements were recorded after 2, 3, 5, 10, 20, and 30 minutes of infusion to assess the onset of peak hemodynamic effects. In later experiments, measurements were recorded at peak steady state (3 minutes of infusion), followed by 10 minutes to allow a return to control before infusion of the subsequent dose. Statistical analysis of the hemodynamic variables at different dose levels was performed using the paired *t*-test or the *t*-test for correlated means.[10]

In some of the experiments, the mechanism of hemodynamic effects of this agent was studied by measuring responses to a single intravenous infusion of carnitine (40 mg/kg per minute) in the following subgroups. Subgroup 1: four animals; beta-adrenergic blockade was produced by an intravenous bolus of propranolol 1 mg/kg. Subgroup 2: three animals; cholinergic blockade was produced by an intravenous bolus of atropine 0.1 mg/kg. Subgroup 3: three animals; the catecholamine-depleted dog induced by pretreatment with an intraperitoneal injection of reserpine (0.75 mg/kg) 18 hours prior to the experiment.

## Results

Responses of selected hemodynamic parameters to doses of carnitine infusion are shown in Table I. It can be seen that at the lower infusion rate of 20 mg/kg per minute, hemodynamic responses were minimal and essentially insignificant. At 40 mg/kg per minute, there was a definite increase in stroke volume and cardiac output attended by a slight compensatory bradycardia. End-diastolic pressure in the left ventricle was mildly elevated, rising to the upper limits of normal, and left ventricular contractile force dropped slightly. At this dose, the dilating effect on the pulmonary, coronary, and systemic vascular beds was quite apparent and significant.

Figure 1 is a graphic representation of selected hemodynamic parameters in terms of per cent change from control over the most effective infusion rates (30–60 mg/kg per minute). Some parameters reached significant levels at 30 mg/kg per minute; and with most parameters, optimal levels were evident at 40 mg/kg per minute. The mean changes in calculated systemic, pulmonary, and coronary vascu-

**TABLE I**

**Hemodynamic Dose Responses to Carnitine Infusion†**

| | Control | 20 mg/kg/min | Control | 40 mg/kg/min | Control | 60 mg/kg/min |
|---|---|---|---|---|---|---|
| HR (beats/min) | 113±9.6 | 108±8.8 | 129.0±17.2 | 113.8±17.3* | 124.3±16.2 | 86.0±13.0** |
| $\overline{m}$AoP (mm Hg) | 92.6±8.7 | 88.3±11 | 106.8±16.4 | 97.5±13.5 | 114.2±9.2 | 98.1±6.4* |
| SV (ml/beat) | 10.8±1.2 | 12.6±1.6 | 8.9±1.9 | 15.8±3.5** | 8.7±0.9 | 17.2±1.4** |
| LVED (mm Hg) | 2.5±0.5 | 3.0±0.4 | 3.8±0.63 | 6.2±0.48* | 4.0±0.58 | 11.3±2.40** |
| LVCF (%C) | 100 | 95.2±7.1 | 100±0 | 85±10.1* | 100±0 | 138±15** |
| LV *dp/dt* (mm Hg/sec) | 1201±108 | 1190±98 | 1330±114 | 1438±161 | 1366±178 | 1986±177* |
| $\overline{m}$PAP (mm Hg) | 14.2±1.5 | 14.9±1.6 | 14.7±1.3 | 18.6±2.2* | 13.3±1.2 | 17.6±2.2* |
| LCBP ml/min) | 22.1±1.9 | 23.0±1.8 | 20.2±2.3 | 28.2±2.9* | 25.2±3.1 | 59.2±6.1** |
| $\overline{m}$AoF (l/min) | 1.3±0.2 | 1.4±0.2 | 1.2±.14 | 1.91±.18* | 1.1±.09 | 1.5±.17* |

† *t*-test; * $P<0.05$; ** $P<0.001$; HR=heart rate; $\overline{m}$AoP=mean aortic pressure; SV=stroke volume; LV=left ventricular; LVED=LV end-diastolic pressure; LVCF=LV contractile force; LV *dP/dt*=peak rate of rise of LV pressure; $\overline{m}$PAP=mean pulmonary arterial pressure; LCBF=left circumflex coronary blood flow; $\overline{m}$AoF=mean aortic flow. All values are means ± S.E.M.

lar resistances during infusion of carnitine confirm the vasodilating properties of carnitine upon these three vascular beds over this dose range.

Figure 2 shows the time course of changes in a representative experiment at an infusion of 40 mg/kg per minute. It can be seen that with the beginning of infusion, there is moderate lowering of aortic pressure with a widening of pulse pressure, an increase in aortic flow, and an increase in left circumflux coronary blood flow. There is also a rise in end-diastolic pressure, no doubt reflecting the increased left ventricular end-diastolic volume. This is also attended by an increase in left ventricular *dP/dt* despite the drop in heart rate and afterload. These responses are compatible with the combined effect of peripheral vasodilation and a cardiac inotropic effect.

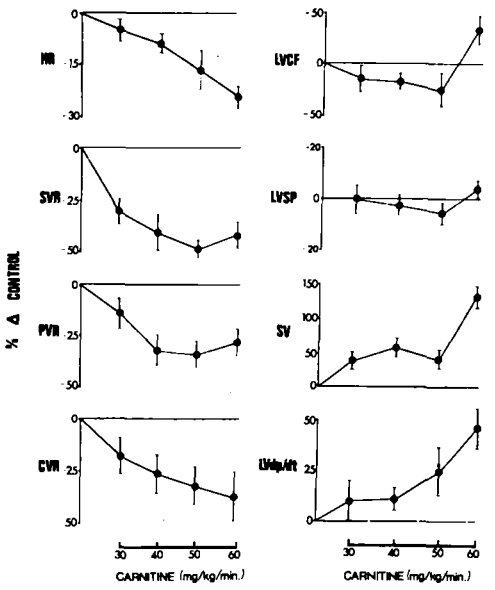


*Fig. 1. Per cent changes (means ± S.E.) of selected hemodynamic responses over the more effective dose range of carnitine infusion. A dose-related vasodilating effect is quite evident. HR = Heart rate (per minute); CVR, PVR, and SVR = coronary, pulmonary, and systemic vascular resistances, respectively (dynes • sec • cm$^{-5}$); LV = left ventricular; CF = contractile force (% control); SP = systolic pressure (mm Hg); dP/dt = rate of rise of LV pressure (mm Hg/sec) EDP = end-diastolic pressure (mm Hg). Other abbreviations as in Table I.*

At the higher infusion rate of 60 mg/kg per minute (Table I), heart rate fell from 124 to 86 beats/minute, and stroke volume essentially doubled. End-diastolic pressure rose from 4.0 to 11.3 mm Hg, and left ventricular *dP/dt* increased from 1366 to 1986 mm Hg/sec. This increase in cardiac contraction is confirmed by an increase in left ventricular contractile force of 38 per cent above control. Left coronary blood flow increased from 25.2 to 59.2 ml/minute, reflecting the increased coronary demands and lowered coronary resistance. The infusion at these higher doses was frequently attended by ventricular arrhythmias—usually frequent premature ventricular contractions, often two and three in a row. At doses higher than 60 mg/kg per minute, there were more arrhythmias, and ventricular dilation was observed. In three instances, ventricular fibrillation occurred after 15 minutes of continuous infusion of 70 mg/kg per minute. No significant dysrhythmias developed at the moderate or lower doses.

Figure 3 shows the changes in stroke volume before and after beta-blockade with propranolol and parasympathetic blockade with atropine, and the effect in the reserpinized animal. It is apparent that there was no attenuation of any of the control responses following these interventions.

## Discussion

These studies have shown carnitine to be a potent vasoactive compound in the normal intact animal. At smaller doses (20 mg/kg per minute and below), there are minimal hemodynamic effects which are variable and rarely significant. The

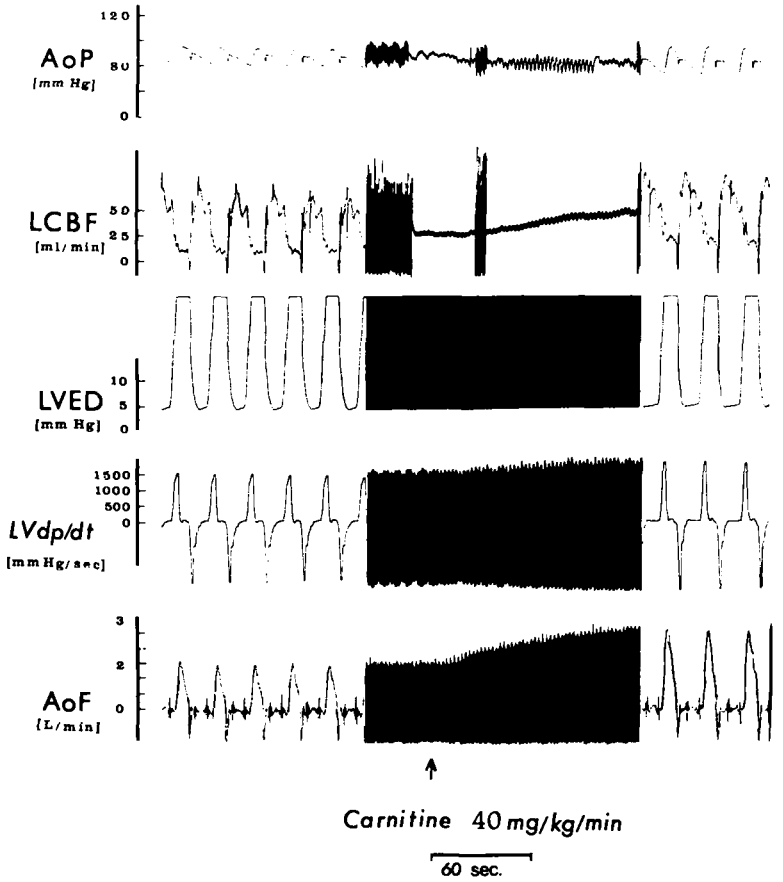


*Fig. 2. Selected hemodynamic data from a representative animal during a carnitine infusion of 40 mg/kg per minute. Onset is fairly rapid, so that peak effects are achieved within 1.5 to 2 minutes. Abbreviations as in Table I.*

hemodynamic effects appear to be the result of both a direct vasodilation and of a positive inotropic response. At moderate infusion rates of 30 and 40 mg/kg per minute, there is primarily a vasodilating effect evidenced by increased flow, widened pulse pressure, and decreased resistances in coronary, pulmonary, and systemic vascular beds. At higher doses of 50 and 60 mg/kg per minute these vasodilating effects are accompanied by a positive inotropic effect. The onset of action by carnitine is fairly rapid, and its effect is transient, promptly disappearing as the infusion is discontinued. Likewise bolus injections induce brief, dose-related effects. Dysrhythmias are uncommon at the small and moderate doses but are quite frequent and severe at the higher doses.

The mechanism of this vasodilator action by carnitine is not well understood. Recent studies by Vick and Defelice[3] indicate that it was rapidly absorbed across cell membranes and acted directly on the smooth muscle of the blood vessels. It reversed the action of palytoxin, an intense vasoconstrictor agent, by rapid injection directly into the ventricles of the test animal. Papaverine had a similar effect but

was not as potent in this regard as carnitine.[3] It was postulated that death by palytoxin is due to profound coronary vasoconstriction and subsequent cardiac failure. This palytoxin constrictor effect appears to be directly on the smooth muscle in the blood vessel wall. Carnitine's reversal of this effect was only present when injected directly into the ventricles, indicating a rapid onset of a protective vasodilator action on vascular smooth muscle in these animals.

The vasoactive effect was clear-cut in the present experiments. It was dose related, becoming increasingly evident at the higher levels of infusion. The effect was not blocked by propranolol or by atropine, and it was still present in the reserpinized, catecholamine-depleted animal. This series of findings essentially rules out an adrenergic or cholenergic mechanism. The extremely high tissue levels of carnitine in adrenal tissue (6.4 times that of heart and 12.0 times that in striated muscle, over 20 times that of most other tissues[2]), taken together with its rapid onset of action and potent vasodilator effect, imply an important role in meeting stress-related demands upon cardiovascular dynamics.

The coronary vascular effect is of particular interest. The dilator response was unequivocal, as evidenced by increased coronary flow at a decreased perfusion pressure and a decrease in calculated coronary vascular resistance. It is not possible to know from these data whether this effect was a primary vasodilator response or was secondary to the increased demands on the myocardium. Small doses injected locally into the cannulated coronary artery or in vitro studies involving coronary arterial muscle strips will be required to answer this question. However, these data in the intact animal indicate that the dilator effect is certainly adequate for the demands, since at the dose where vasodilation was maximal, inotropic effects were minimal and the heart rate was reduced from control levels. This constitutes a relatively small load on the heart at a time when coronary flow has essentially doubled and coronary vascular resistance has decreased by 40 per cent.

At higher doses, the vasoactive properties of carnitine were accompanied by

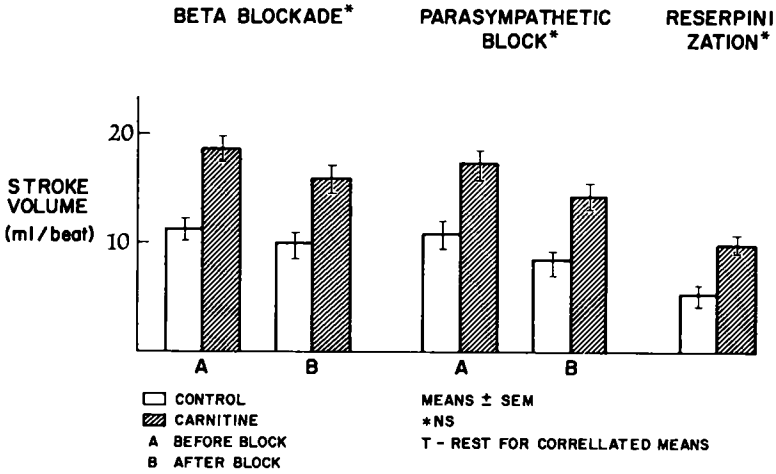


*Fig. 3. Effects of carnitine on stroke volume before and after blockade with propranolol and atropine and in the reserpinized animal. There is essentially no change in the responses after blockade.*

increasing evidence of a direct positive inotropic effect. Although sometimes difficult to assess in the intact animal, the evidence for this enhanced contractile response is the direct increase in left ventricular contractile force at the higher doses as well as the increase in left ventricular *dP/dt*. It is true that this increased contraction was accompanied by an increase in left ventricular size and left ventricular end-diastolic pressure; however, it was also accompanied by a reduction in heart rate and a drop in afterload. Both of the latter parameters would tend to negate any gains in contraction derived from an increase in heart size and end-diastolic stretch. At the very highest doses of 70 mg/kg per minute, the predominant effect was that of an increase in contraction, an increase in peak and mean arterial pressure, and an increase in heart size. This state was difficult to maintain because of serious ventricular dysrhythmias and was clearly beyond any therapeutic range.

The previous reports of efficacious effects of carnitine at lower doses than those used in these experiments are of interest. Thomson et al.[8] found that doses of 20 and 40 mg/kg as a single bolus were effective in improving stress tolerance of the ischemic myocardium in patients with stable coronary artery disease. The reason for this difference in dose response is not clear. While it may be species related, it has also been shown in the isolated heart that the myocardial pool of carnitine fluctuates in relation to changes in the energy requirements of the heart.[11] Further, exogenous carnitine enhances the immediate sources of energy (ATP, creatinine) for muscle contraction.[12] On the other hand, it inhibits the overactivity of tissue in the hyperthyroid state.[13,14] It is also demonstrated that fatty acid transport and subsequent oxidation in cardiac mitochondria is mediated through carnitine-dependent pathways, with fuel as a byproduct.[4,12] Furthermore, the effect of carnitine on fatty acid utilization has been shown in vivo, using an intact dog heart.[15,16] All of these data indicate that the effectiveness of carnitine may be more evident in energy-depleted states or under hypoxic conditions and that the higher doses required to produce a vasoactive and inotropic effect in the normal intact dog heart in these experiments is related to the relative lack of need for available energy substrate.

## Summary

Direct cardiac as well as systemic, coronary, and pulmonary vascular responses to intravenous infusions of carnitine at doses ranging from 10 to 70 mg/kg per minute were measured in 22 open-chest, chloralose-anesthetized mongrel dogs. Aortic and left circumflex coronary blood flow was measured by electromagnetic flowmeter; left ventricular (LV) contractile force, by isometric strain gauge on the LV free wall; pulmonary aortic pressures, through catheters; and LV pressure and its rate of rise (LV *dP/dt*), through a Teflon needle in the LV apex. Steady-state responses were measured at 3, 5, 10, and 20 minutes of infusion. Onset of action was fairly rapid, with peak response achieved within 3 minutes. Responses were dose related with only minor effects at lower infusion rates—20 mg/kg per minute and below. Optimal hemodynamic responses occurred at 40 mg/kg per minute, where there was evidence of moderate vasodilation of coronary, pulmonary, and systemic vascular beds and minimal inotropic effects. At higher doses, there were distinct additional inotropic effects. These responses were not significantly altered by high-dose propranolol pretreatment or in reserpinized dogs, which essentially excludes a catecholamine-induced mechanism. We conclude that carnitine is a potent nonadrenergic agonist with both vascular dilating and

inotropic effects in the normal intact heart.

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