Effect of L-Carnitine on Cardiac Hemodynamics

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SUMMARY

The effect of L-carnitine on cardiac hemodynamics was evaluated in normal closed chest dogs. Extracorporeal circulation was produced to measure coronary blood flow in closed chest dogs. Coronay venous blood was introduced to the extracorporeal circuit through a polyethylene catheter wedged into the coronay sinus under fluoroscopic control and was returned to the animal through the left jugular vein. L-carnitine was infused intravenously at a constant rate of 80 mg/Kg/min for 8 min. Hemodynamic responses appeared within 1 to 3 min of carnitine infusion and peak effects were observed nearly after 5 min. Peak effects on cardiac hemodynamics after 5 to 8 min of carnitine infusion were as follows. Heart rate decreased by 17% from control ($p<0.05$). Aortic and left ventricular pressure increased by 20% ($p<0.05$ and $p<0.01$ respectively) and peak positive left ventricular dp/dt increased by 35% ($p<0.01$), the mean rate pressure product as the index of myocardial oxygen consumption remained unchanged. Coronary blood flow increased by 60% ($p<0.001$) and coronary vascular resistance decreased by 25% ($p<0.01$). As the infusion of carnitine was discontinued, the effects promptly disappeared. These data suggest that L-carnitine has direct vasodilating and positive inotropic effects on cardiovascular system.

Additional Indexing Words:

Normal closed chest dog Direct vasodilating effect Positive inotropic effect Myocardial oxygen consumption

FREE fatty acids at high concentrations have been shown to impair myocardial cellular functions,[1)-6)] whereas they are a major metabolic fuel of the heart.[7),8)] Recently, considerable attention has been focused on the role of carnitine in impaired fatty acid metabolism in ischemic myocardium,[9)-15)] because carnitine is essential for long chain fatty acids to be transported to the sites of oxidation in the mitochondria.[16),17)]

Carnitine is a water-soluble naturally occurring amino acid with the following formula:

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Received for publication April 28, 1980.

$$(CH_3)_3N^+CH_2 \cdot CH(OH) \cdot CH_2 \cdot COO^-.$$

It is synthesized from lysine largely in the liver and transported to most of tissues of the body including heart and skeletal muscle.[18]

Protective effects of exogenous carnitine on metabolic derangements in ischemic hearts have been demonstrated in several reports,[12),14),15] but hemodynamic effect of carnitine has been reported only in normal open chest dogs using DL-carnitine.[19] However D-form of carnitine not only has no biological effects but also competitively inhibit the uptake of L-carnitine to tissues.[20]

The purpose of this study was to evaluate the effect of L-carnitine on cardiac hemodynamics in normal closed chest dogs.

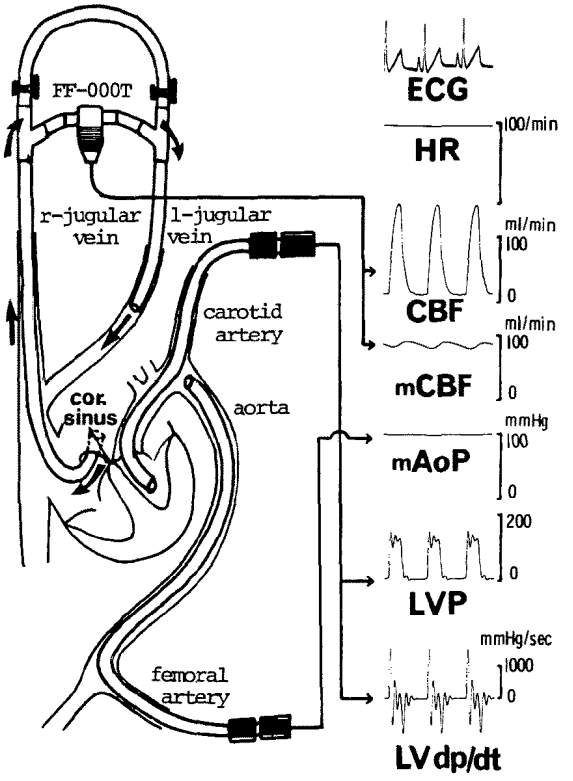

Fig. 1. Schematic diagram of dog preparation. Extracorporeal circulation was produced to measure coronary blood flow in closed chest dogs. Coronary venous blood was introduced to the extracorporeal circuit through a polyethylene catheter wedged into the coronary sinus and was returned to the animal through the left jugular vein. Electrocardiogram (ECG), heart rate (HR), pulsatile and mean coronary blood flow (CBF and mCBF), mean aortic pressure (mAoP), left ventricular pressure (LVP), and the first derivative of left ventricular pressure (LV dp/dt) were recorded simultaneously on a multichannel recorder as shown on the right.

Materials and Methods

Five mongrel dogs weighing 8 to 10 Kg were anesthetized with intravenous sodium pentobarbital (30 mg/Kg body weight).

Extracorporeal circulation was produced to measure coronary blood flow in closed chest dogs (Fig. 1). Coronary venous blood was introduced to the extracorporeal circuit through a polyethylene catheter (inside diameter 5 mm) wedged into the coronary sinus under fluoroscopic control and was returned to the animal through the left jugular vein. An electromagnetic flow probe (Nihon Kohden FF-000T) was placed around the proximal circuit and blood flow was measured with pulsed wave flowmeter (Nihon Kohden MF-27). Zero reference was obtained by occluding the proximal circuit at both sides of the probe and mean and pulsatile coronary blood flow was recorded by occluding the distal circuit.

Left ventricular and aortic pressure was measured through Cournand 8F catheters inserted into left ventricle and aorta via left carotid and left femoral arteries respectively and connected to Nihon Kohden MPU-0.5 pressure transducer.

L-carnitine (provided by Otsuka Pharmaceutical Factory Inc, Japan) was infused intravenously at a constant rate of 80 mg/Kg/min for 8 min.

Electrocardiogram (ECG), heart rate (HR), pulsatile and mean coronary blood flow (CBF and mCBF), mean aortic pressure (mAoP), left ventricular pressure (LVP), and the first derivative of left ventricular pressure (LV dp/dt) were recorded simultaneously on a multichannel recorder.

Left ventricular dp/dt was used as the index of ventricular contractile force and mean rate pressure product (HR$\times$mAoP) was used as the index of myocardial oxygen consumption. Coronary vascular resistance was calculated by mAoP/mCBF.

Statistical analysis of the hemodynamic variables was performed using Student's paired *t*-test.

Results

The effects of L-carnitine on various hemodynamic parameters were shown in Figs. 2 and 3 in terms of percent change of control.

Hemodynamic responses appeared within 1 to 3 min of carnitine infusion and peak effects were observed nearly after 5 min. After 5 to 8 min of carnitine infusion, heart rate decreased by 17% from control value. Aortic and left ventricular pressure increased by 20% and peak positive LV dp/dt increased by 35%, whereas mean rate pressure product as the index of myocardial oxygen consumption remained unchanged. Coronary blood flow increased by 60% and coronary vascular resistance decreased by 25%. As the infusion of carnitine was discontinued, the effects promptly disappeared except the increase in coronary blood flow and the decrease in coronary vascular resistance.

In a case shown in Fig. 4, premature ventricular contractions that hap-

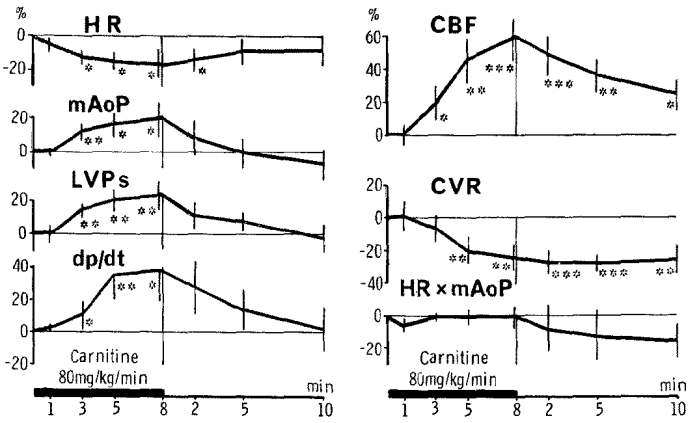

Fig. 2. Effect of L-carnitine on cardiac hemodynamics. L-carnitine was infused intravenously at a rate of 80 mg/Kg/min. Hemodynamic parameters were shown in terms of percent change of control. Values are represented as the mean±SD. Statistical analysis of the hemodynamic variables was performed using Student's paired t-test (* $p<0.05$, ** $p<0.01$, *** $p<0.001$).

Abbreviations: HR=heart rate; mAoP=mean aortic pressure; LVPs=systolic left ventricular pressure; dp/dt=left ventricular dp/dt; CBF=coronary blood flow; CVR=coronary vascular resistance.

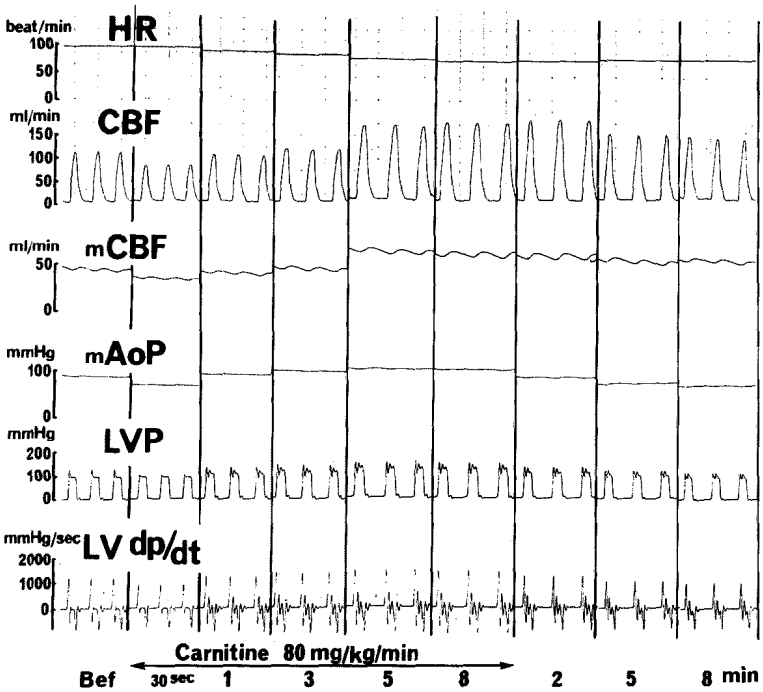

Fig. 3. Hemodynamic data from a representative animal during infusion of L-carnitine at a rate of 80 mg/Kg/min. Abbreviations as in Fig. 1.

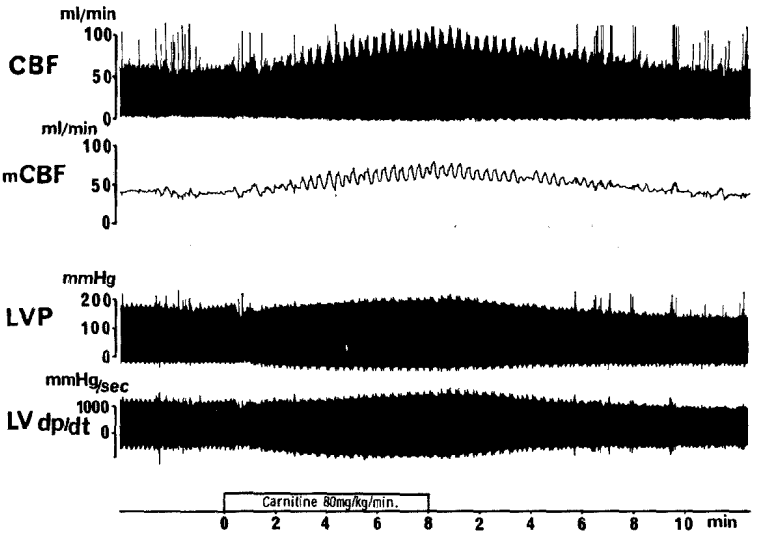

Fig. 4. Effect of L-carnitine on ventricular arrhythmias in an animal. Sharp spikes observed on the record of CBF and LVP represent premature ventricular contractions. Hemodynamic responses are similar to those in Fig. 3. Abbreviations as Fig. 1.

pened to be present in the control period disappeared during carnitine infusion and reappeared after the discontinuation of the infusion.

Discussion

As a cause of toxic effects of high plasma free fatty acids, accumulation of long chain acyl CoA has been proposed.[11] Since high levels of long chain acyl CoA inhibits adenine nucleotide translocase activity[21)-23)] that is the regulator of the egression of ATP across the inner mitochondrial membrane, ATP production in ischemic myocardium is limited both by the reduced supply of oxygen and by the accumulated long chain acyl CoA. L-carnitine 100 mg/Kg that was administered intravenously prior to coronary artery ligation prevented the accumulation of long chain acyl CoA and ATP depletion in ischemic myocardium and serious ventricular arrhythmias in early phases of myocardial ischemia.[15]

Hemodynamic effects of L-carnitine were evaluated in this study at a dose of 80 mg/Kg/min, because only minimal hemodynamic changes were observed at smaller doses (20 and 40 mg/Kg/min) although metabolic improvement had been observed in ischemic myocardium.[15]

The most pronounced response was found in the increase in coronary blood flow. Since it was accompanied by the decrease in coronary vascular

resistance and mean rate pressure product as the index of myocardial oxygen consumption remained unchanged, the increase in coronary blood flow is supposed to be due to the direct vasodilating effect on coronary vascular bed. The increase in left ventricular dp/dt despite the drop in heart rate indicates that L-carnitine has a positive inotropic effect, and the reduced heart rate may result from the reflex to the increase in left ventricular pressure.

The onset of hemodynamic responses to L-carnitine was very rapid and the effects promptly disappeared as the infusion was discontinued. And these effects were not observed at lower doses although metabolic improvement had been demonstrated. Therefore the hemodynamic changes observed in this study appear to result not from the improvement of fatty acid metabolism that is the most important property of carnitine, but from direct pharmacological effects on cardiovascular system. Although the mechanism of the effects is not well understood, it has been demonstrated that the vasodilating effect was not blocked by propranolol or by atropine and it was still present in the reserpinized catecholamine depleted animal.[19]

On the study using DL-carnitine, frequent premature ventricular contractions have been reported to occur at doses higher than 60 mg/Kg/min, whereas no significant dysrhythmias developed at the moderate or lower doses.[19] In this study using L-carnitine, on the other hand, no arrhythmias were observed during the infusion of L-carnitine at a rate of 80 mg/Kg/min and premature ventricular contractions that happened to be present before carnitine infusion disappeared during the infusion.

The administration of exogenous carnitine has been demonstrated to prevent ATP depletion in ischemic myocardium and serious arrhythmias in early phases of myocardial infarction.[14),15] And these effects are supposed to result from improvement of impaired fatty acid metabolism. Catecholamines most widely used today for cardiogenic shock not only to increase myocardial oxygen consumption but also to stimulate lipolysis, resulting in high plasma free fatty acids. And those metabolic changes are supposed to exaggerate ischemic damage of myocardium.

Taking these observations into considerations, the results in this study suggest that L-carnitine may be beneficial for the treatment of cardiogenic shock not only from metabolic but also hemodynamic point of view.

References

1. Kurien VA, Yates PA, Oliver MF: The role of free fatty acids in the production of ventricular arrhythmias after acute coronary artery occlusion. Eur J Clin Invest **1**: 225, 1971
2. Henderson AH, Most AS, Parmley WW: Depression of myocardial contractility in rats by free fatty acids during hypoxia. Circulat Res **26**: 439, 1970

3. Kjekshus JK, Mjøs OD: Effect of free fatty acids on myocardial function and metabolism in ischemic dog heart. J Clin Invest **51**: 1767, 1972
4. Willebrands AF, Ter Welle HF, Tasseron SJA: The effect of a high molar FFA/albumin ratio in the perfusion medium on rhythm and contractility of the isolated rat heart. J Mol Cell Cardiol **5**: 259, 1973
5. Yamazaki N, Suzuki Y, Kamikawa T, Ogawa K, Mizutani K, Kakizawa N, Yamamoto M: Arrhythmogenic effects of acute free fatty acid mobilization on ischemic heart. Recent Advances in Studies on Cardiac Structure and Metabolism, Vol 12, Cardiac Adaptation, University Park Press, Baltimore, p 271, 1978
6. Liedtke AJ, Nellis S, Neely JR: Effects of excess free fatty acids on mechanical and metabolic function in normal and ischemic myocardium in swine. Circulat Res **43**: 652, 1978
7. Bing RJ: Cardiac metabolism. Physiol Rev **45**: 171, 1965
8. Opie LH: Metabolism of the heart in health and disease. Part I. Am Heart J **76**: 685, 1968
9. Schwartz A, Wood JM, Allen JC, Bornet EP, Entman ML, Goldstein MA, Sordahl LA, Suzuki M, Lewis RM: Biological and morphological correlates of cardiac ischemia. 1. Membrane Systems. Am J Cardiol **32**: 46, 1973
10. Shug AL, Shrago E: A proposed mechanism for fatty acid effects on energy metabolism of the heart. J Lab Clin Med **81**: 214, 1973
11. Shrago E, Shug AL, Sul H, Bittar N, Folts JD: Control of energy production in myocardial ischemia. Circulat Res **38** (Suppl 1): 75, 1976
12. Shug AL, Thomsen JH, Folts JD, Bittar N, Klein KI, Koke JR, Huth PJ: Changes in tissue levels of carnitine and other metabolites during myocardial ischemia and anoxia. Arch Biochem Biophys **187**: 25, 1978
13. Whitmer JT, Idell-Wenger JA, Rovetto MJ, Neely JR: Control of fatty acid metabolism in ischemic and hypoxic heart. J Biol Chem **253**: 4305, 1978
14. Folts JD, Shug AL, Koke JR, Bittar N: Protection of ischemic myocardium with carnitine. Am J Cardiol **41**: 1209, 1978
15. Suzuki Y, Kamikawa T, Kobayashi A, Yamazaki N: Protective effects of L-carnitine on the energy metabolism in ischemic myocardium. J Mol Cell Cardiol **11** (Suppl 3): 29, 1979
16. Fritz IB, Kaplan E, Yue KTN: Specificity of carnitine action on fatty acid oxidation by heart muscle. Am J Physiol **202**: 117, 1962
17. Pande SV: A mitochondrial carnitine acylcarnitine translocase system. Proc Nat Acad Sci USA **72**: 883, 1975
18. Tanphaichitr V, Broquist HP: Site of carnitine biosynthesis in the rat. J Nutr **104**: 1669, 1974
19. Brooks H, Goldberg L, Holland R, Klein M, Sanzari N, DeFellice S: Carnitine-induced effects on cardiac and peripheral hemodynamics. J Clin Pharm **17**: 561, 1977
20. Mölstad P, Böhmer T, Eiklid K: Specificity and characteristics of the carnitine transport in human heart cells (CCL 27) in culture. Biochim Biophys Acta **471**: 296, 1977
21. Pande SV, Blanchaer MC: Reversible inhibition of mitochondrial adenosine diphosphate phosphorylation by long chain acyl coenzyme A esters. J Biol Chem **246**: 402, 1971
22. Shug AL, Lerner E, Elson C, Shrago E: The inhibition of adenine nucleotide translocase by oleoyl CoA and its reversal in rat liver mitochondria. Biochem Biophys Res Commun **43**: 557, 1971
23. Harris RA, Farmer B, Ozawa T: Inhibition of the mitochondrial adenine nucleotide transport system by oleoyl CoA. Archiv Biochem Biophys **150**: 199, 1972