

# EFFECTS OF L-CARNITINE ON VENTRICULAR ARRHYTHMIAS IN DOGS WITH ACUTE MYOCARDIAL ISCHEMIA AND A SUPPLEMENT OF EXCESS FREE FATTY ACIDS

YOSHIKAZU SUZUKI, M.D., TADASHI KAMIKAWA, M.D.  
AND NOBORU YAMAZAKI, M.D.

The effects of L-carnitine on ventricular arrhythmias were evaluated in dogs with acute myocardial ischemia and a supplement of excess free fatty acids (FFA).

Acute myocardial ischemia was induced by ligation of left anterior descending coronary artery. After 80 minutes of coronary occlusion, high plasma FFA was induced by intravenous injection of heparin 200 u/kg and Intralipid® 5 ml/kg as a bolus. After additional 60 minutes, beating hearts were removed from animals and tissue levels of free carnitine, short and long chain acyl carnitine, FFA and adenosine triphosphate (ATP) were determined. L-carnitine 100 mg/kg was administered intravenously 5 minutes before coronary artery ligation. Electrocardiograms were recorded continuously by a Holter electrocardiographic recorder during the experiment and ventricular arrhythmias were quantified by an arbitrary scoring system.

In ischemic and excess FFA supplemented myocardium, free carnitine and ATP decreased, whereas long chain acyl carnitine and FFA increased. And these metabolic changes tended to be reduced by L-carnitine. Pretreatment of L-carnitine also reduced the grade of ventricular arrhythmias induced both by acute myocardial ischemia and by supplement of excess FFA.

These results suggest that the administration of L-carnitine may be beneficial to prevent serious arrhythmias in ischemic heart disease, presumably by restoring the impaired FFA oxidation.

**H**IGH concentrations of free fatty acids (FFA) have been reported to provoke some arrhythmias in ischemic heart disease.<sup>1-3</sup>

## Key Words:

L-carnitine  
Ventricular arrhythmias  
Acute myocardial ischemia  
Excess free fatty acids  
Long chain acyl carnitine

Several explanations have been proposed concerning the mechanism, such as nonspecific detergent action on biomembranes which leads to cation loss<sup>4</sup> followed by the changes of action potential<sup>5-7</sup> and uncoupling of oxidative phosphorylation in the mitochondria<sup>8-11</sup> which leads to the reduced production of adenosine triphosphate (ATP). However, recently, a great attention has been focused on the accumulation of inter-

(Received July 29, 1980; accepted December 11, 1980)

The Third Department of Internal Medicine, Hamamatsu University, School of Medicine, Hamamatsu, Japan

Presented in part at the 50th Tokai Regional Meeting of the Japanese Circulation Society in Hamamatsu, Nov. 17, 1979 and at the 7th Asian-Pacific Congress of Cardiology in Bangkok, Nov. 25, 1979.

Address for reprints: Yoshikazu Suzuki, M.D., The Third Department of Internal Medicine, Hamamatsu University, School of Medicine, 3600 Handa-cho, Hamamatsu 431-31, Japan

mediates subsequent to impaired oxidation of FFA as a cause of the toxic cardiac effects of excess FFA.<sup>12-15</sup>

Carnitine, a water-soluble naturally occurring amino acid, is essential for fatty acyl derivatives to penetrate across the inner mitochondrial membrane<sup>16,17</sup> and to be transported to the sites of oxidation in the mitochondria. A reduction in tissue levels of carnitine has been demonstrated in ischemic<sup>18-21</sup> and FFA supplemented heart<sup>14</sup> and is supposed to exaggerate ischemic damage of myocardium, presumably by accelerating the accumulation of fatty acyl derivatives. From this point of view, protective effects of exogenous carnitine on the metabolic derangement in ischemic heart have been reported in several studies.<sup>19,21-23</sup> However, antiarrhythmic effects of exogenous carnitine have been reported only in the incidence of protection against ventricular fibrillation in the dogs with coronary artery occlusion.<sup>21,22</sup>

The purpose of this study was to evaluate the effects of L-carnitine on the ventricular arrhythmias in the dogs with acute myocardial ischemia and a supplement of excess FFA.

## MATERIALS AND METHODS

Twenty-one mongrel dogs weighing 8 to 12 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Ventilation was maintained by means of a Harvard animal respirator with room air. The dogs had been fasted for 16 to 20 hours. A left thoracotomy was performed through the 4th intercostal space. The pericardium was opened and the heart was exposed. Pericardial cut edges were fastened to the perimeter of the sternal opening and heart was slightly suspended. A short area of the left anterior descending branch of the coronary artery was dissected free from surrounding tissue and the dissected artery was ligated by a silk thread together with 23 gage needle located beside it. By drawing off the needle, incomplete occlusion of coronary artery was produced. After 80 minutes of coronary ligation, a bolus of 200 u/kg of heparin and 5 ml/kg of Intralipid® containing soy-bean oil were injected intravenously. After additional 60 minutes, beating hearts were removed from the animals and transmural tissue (1-1.5g) representing ischemic area (supplied by the ligated artery) and nonischemic area (supplied by circumflex artery) were rapidly excised. Briefly the respective tissues were frozen with Wollenberger

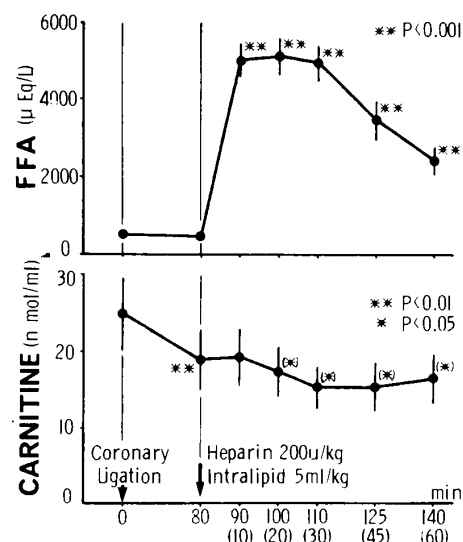


Fig.1. Effects of coronary ligation and administration of heparin and Intralipid on the plasma levels of FFA and carnitine. About carnitine, asterisks without parenthesis represent the significance of change with respect to the level before coronary ligation. Asterisks inside the parenthesis represent the significance of change with respect to the level after 80 minutes of coronary ligation.

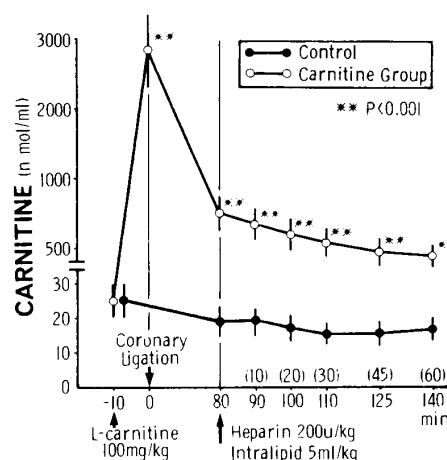


Fig.2. Plasma levels of carnitine in dogs pretreated with 100 mg/kg of L-carnitine (carnitine group). Asterisks represent the significance of change with respect to the control levels.

clamp cooled to the temperature of liquid nitrogen. The frozen and pressed samples were cracked into fragments on a block of dry ice and stored at  $-70^{\circ}\text{C}$ . Extraction and analysis of carnitine, short and long chain acyl carnitine, ATP and FFA were made on these frozen tissues within three days. Plasma levels of carnitine and FFA were determined before and after 80 minutes

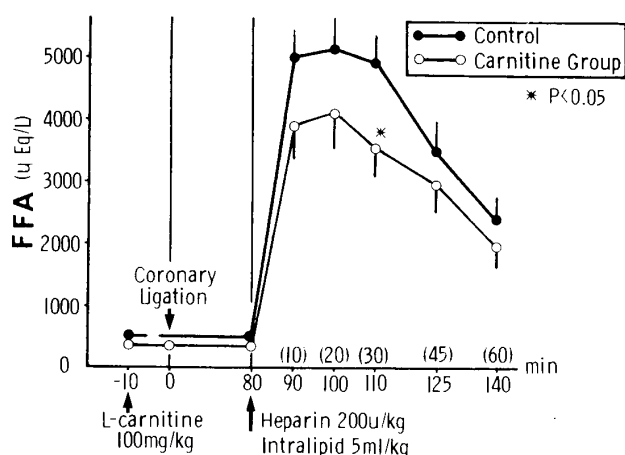


Fig.3. Effect of L-carnitine on the plasma levels of FFA. An asterisk represents the significance of change with respect to the control level.

of coronary ligation and at 10, 20, 30, 45 and 60 minutes after the injection of heparin and Intralipid.

Electrocardiograms were recorded continuously during the experiment by a Holter electrocardiographic recorder and analysed by DYNAGRAM Model DCG-6000 (Instrument for Cardiac Research Inc., New York).

In ten dogs, 100 mg/kg of L-carnitine (provided by Otsuka Pharmaceutical Factory Inc., Japan) was administered intravenously over five minutes. After additional five minutes, the coronary artery was ligated. Eleven dogs without L-carnitine were used as the controls.

Free carnitine was determined enzymatically using carnitine acetyl transferase by the method of Marquis and Fritz<sup>24</sup>. Short and long chain acyl carnitine were assayed as free carnitine after alkaline hydrolysis by the method of Pearson et al.<sup>25</sup>. ATP was determined by enzyme assay using hexokinase and glucose-6-phosphate dehydrogenase<sup>26</sup> and FFA was determined by the method of Itaya and Ui<sup>27</sup>.

Values were represented as mean  $\pm$  SE. Statistical analysis was made by paired or non-paired Student's t test, as appropriate.

## RESULTS

### Plasma levels of FFA and carnitine

Plasma levels of FFA and carnitine in the control dogs are shown in Fig. 1. Plasma FFA remained unchanged after 80 minutes of coronary ligation. Following the injection of heparin and Intralipid, plasma FFA rapidly increased ( $p <$

TABLE I SCORING SYSTEM FOR VENTRICULAR ARRHYTHMIAS

0	No VPBs
1	Isolated unifocal VPBs < 5/min
2	Isolated unifocal VPBs > 5/min
3	Multifocal VPBs
4	Couplets or salvos
5	Early VPBs (R on T)
6	Ventricular tachycardia
7	Ventricular fibrillation

Grading system for VPBs by Lown and Wolf<sup>28</sup> was modified.

VPB = ventricular premature beat

0.001), remained at high levels for 30 minutes and gradually decreased thereafter. Plasma carnitine levels decreased after 80 minutes of coronary ligation ( $p < 0.01$ ), and decreased much more after the injection of heparin and Intralipid.

In the dogs pretreated with 100 mg/kg of L-carnitine, plasma levels of carnitine maintained far higher levels throughout the experiment as compared with that in the controls ( $p < 0.001$ ) (Fig. 2). Pretreatment of L-carnitine suppressed the increase in plasma FFA levels induced by heparin and Intralipid after 30 minutes ( $p < 0.05$ ) (Fig. 3).

### Ventricular arrhythmias induced by acute myocardial ischemia and supplement of excess FFA

Ventricular arrhythmias were quantified by an arbitrary scoring system that was produced by modifying the grading system for ventricular premature beats by Lown and Wolf<sup>28</sup> (Table I). Maximum score during every 10 minutes was expressed in individual cases (Table II) and changes of the mean score were shown in Fig. 4.

In untreated dogs, ventricular arrhythmias occurred in all cases following coronary artery occlusion. They usually begin to appear within a few minutes after coronary ligation, reached at a maximum score and subsided thereafter up to 80 minutes, although three different types of the occurrence were observed in individual cases (Fig. 5). In 10 cases, ventricular arrhythmias occurred only in an early period after coronary ligation and disappeared after 40 minutes. In a case, they increased up to 60 minutes after coronary ligation and subsided after 80 minutes. In 9 cases, they continued up to 80 minutes after coronary ligation. Excess FFA induced by

TABLE II VENTRICULAR ARRHYTHMIAS INDUCED BY CORONARY ARTERY OCCLUSION AND SUPPLEMENT OF EXCESS FFA

Case No.	Weight (kg)	Coronary occlusion								Heparin + Intralipid								min
		↓ 10	20	30	40	50	60	70	80	↓ 10	20	30	40	50	60			
Control																		
1	11	4	4	4	5	5	6	5	0	0	1	1	1	4	4			
2	11	6	6	2	0	0	2	1	1	1	3	4	4	3	6			
4	10	4	2	3	2	2	1	2	4	4	2	4	2	4	4			
6	10	4	7															
8	11	0	0	0	1	4	2	2	4	4	4	4	1	1	2			
10	8	0	0	1	0	0	0	0	1	1	0	0	0	0	0			
12	10	0	2	3	0	2	1	0	0	0	1	4	0	4	1			
14	9	0	0	3	4	3	3	4	4	3	4	6	4	6	4			
16	9	0	0	0	0	0	1	1	0	3	1	4	4	1	4			
18	10	0	1	1	0	0	0	0	1	4	1	4	3	3	3			
20	8	4	6	4	4	3	3	3	6	6	6	4	6	4	3			
L-carnitine treated																		
3	9	0	1	3	4	4	4	4	4	3	4	3	4	4	3			
5	9	0	4	1	2	1	3	4	2	1	3	3	6	1	3			
7	10	0	0	0	0	0	0	0	0	1	0	0	0	0	1			
9	11	0	0	1	1	1	1	1	1	0	0	0	0	0	0			
11	9	0	4	1	1	0	0	1	1	0	1	0	3	3	3			
13	12	0	0	1	1	1	1	1	1	4	1	0	0	0	1			
15	8	1	0	0	1	1	1	3	3	3	3	4	4	4	4			
17	9	0	0	0	1	0	1	3	3	1	1	4	3	4	4			
19	8	4	4	4	3	3	4	1	6	3	1	3	3	3	4			
21	10	0	0	1	0	0	1	1	0	1	0	1	1	1	1			

Maximum score for every 10 minutes was expressed according to the scoring system for ventricular arrhythmias as shown in Table 1.

heparin and Intralipid increased again the grade of ventricular arrhythmias.

Pretreatment of L-carnitine reduced the grade of arrhythmias in early phase of myocardial ischemia (10 to 20 minutes) and the arrhythmias induced by excess FFA. These effects of L-carnitine were more clear in the cases in which every score in a period from 40 to 80 minutes of coronary occlusion was below 2 (Fig. 6).

#### *Tissue levels of carnitine derivatives, FFA and ATP*

Changes in the tissue levels of various metabolites following coronary artery occlusion and supplement of excess FFA are shown in Table III. After 140 minutes of coronary occlusion, free and total carnitine decreased, whereas long chain acyl carnitine increased in ischemic myocardium.

ATP decreased and FFA increased in ischemic myocardium (compared with nonischemic myocardium by paired t test). Pretreatment of L-carnitine 100 mg/kg tended to suppress the decrease in free carnitine from  $525 \pm 62$  to  $651 \pm 65$  nmol/g and ATP from  $1.63 \pm 0.48$  to  $2.31 \pm 0.53$   $\mu$ mol/g in ischemic myocardium. On the other hand, it also tended to suppress the increase in long chain acyl carnitine from  $500 \pm 91$  to  $454 \pm 60$  nmol/g, although those changes were statistically not significant (by non-paired t test).

#### DISCUSSION

Two types of ventricular arrhythmias were observed in this study. One was induced by coronary artery occlusion and the other was provoked

TABLE III EFFECTS OF L-CARNITINE ON TISSUE LEVELS OF VARIOUS METABOLITES

		Carnitine				ATP	FFA
		Free	Short chain acyl	Long chain acyl	Total		
		(n mol/g)	(n mol/g)	(n mol/g)	(n mol/g)	( $\mu$ mol/g)	( $\mu$ Eq/g)
Nonischemic area							
No treatment	(10)	878 $\pm$ 146	415 $\pm$ 31	261 $\pm$ 23	1544 $\pm$ 169	5.26 $\pm$ 0.13	3.89 $\pm$ 0.28
L-carnitine treated	(10)	968 $\pm$ 97	368 $\pm$ 30	213 $\pm$ 26	1551 $\pm$ 116	5.34 $\pm$ 0.17	3.49 $\pm$ 0.30
Ischemic area							
No treatment	(10)	525 $\pm$ 62*	361 $\pm$ 34**	500 $\pm$ 91**	1386 $\pm$ 149*	1.63 $\pm$ 0.48***	4.41 $\pm$ 0.34*
L-carnitine treated	(10)	651 $\pm$ 65***	318 $\pm$ 39	454 $\pm$ 60**	1523 $\pm$ 104**	2.31 $\pm$ 0.53***	4.27 $\pm$ 0.38**

Values are expressed per gram wet tissue weight and represented as mean  $\pm$  SE. The number of animals is given in parenthesis. Asterisks represent the significance of change between nonischemic and ischemic areas. \*\*\* $P < 0.001$ , \*\* $P < 0.01$ , \* $P < 0.05$

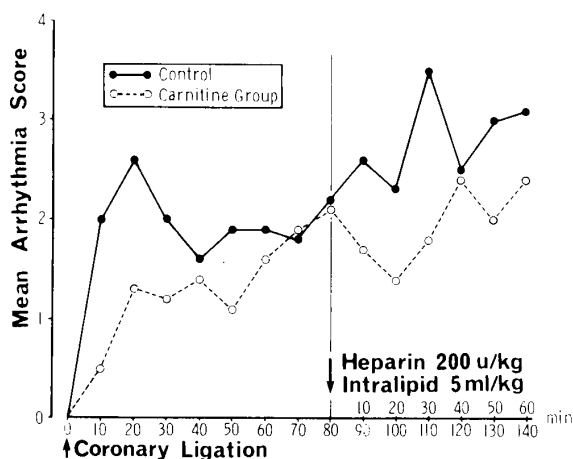


Fig.4. Effect of L-carnitine on the ventricular arrhythmias induced by coronary artery occlusion and supplement of FFA. Effect of L-carnitine on the mean score of ventricular arrhythmias was evaluated in all cases. Scores in 10 minutes after coronary ligation and in 30 minutes after the supplement of excess FFA were significantly reduced by L-carnitine.

ed by the supplement of excess FFA.

#### Early ventricular arrhythmias following coronary artery occlusion

The early ventricular arrhythmias which occur within minutes after coronary artery occlusion has been electrophysiologically explained to result from reentry in ischemic ventricular muscle<sup>29</sup> However, important local metabolic events have been also demonstrated to occur within seconds and minutes of coronary occlusion, namely the increase in extracellular potassium, the in-

crease in tissue lactate, the increase in tissue partial pressure of carbon dioxide followed by marked acidosis and the increase in tissue cyclic adenosine monophosphate (AMP).<sup>30</sup> At the same time, general metabolic changes also occur, namely an increased blood lactate, increased blood FFA concentrations, increased circulating catecholamines and an increased circulating cyclic AMP.<sup>30</sup> And these metabolic factors are thought to play an important role in the genesis of ischemic arrhythmias, probably by causing abnormalities in the action potential of ischemic myocardial cells.<sup>30</sup>

Recently a reduction in tissue levels of carnitine has been demonstrated in ischemic myocardium<sup>18-21</sup> and the accumulated intermediate metabolites in FFA oxidation has been proposed as a cause of the cellular damage in ischemic myocardium.<sup>13</sup>

In our previous study,<sup>31</sup> after 15 minutes of coronary occlusion, tissue levels of free carnitine decreased by 40 percent in ischemic myocardium, whereas long chain acyl carnitine and long chain acyl coenzyme A (CoA) increased by 133 percent and 48 percent respectively. And pretreatment of L-carnitine significantly prevented the depletion in tissue levels of free carnitine and ATP, and the accumulation of long chain acyl carnitine and long chain acyl CoA. In this study, however, no significant changes by L-carnitine were observed in the tissue levels of metabolites, although L-carnitine tended to suppress the decrease in free carnitine and ATP, and the increase in long chain acyl carnitine. The supposed reason is that coronary occlusion of 140 minutes

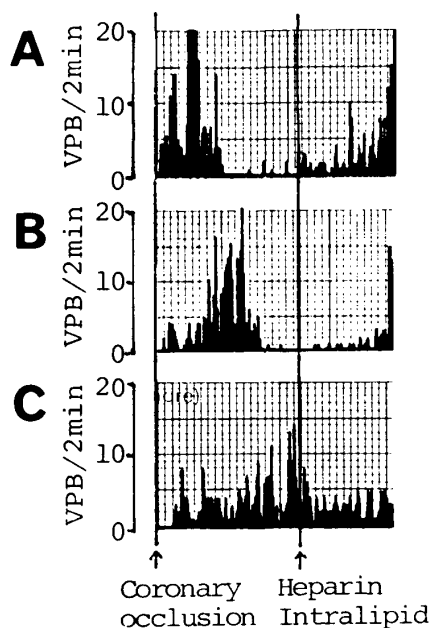


Fig.5. Examples of ventricular arrhythmias induced by coronary artery occlusion and supplement of excess FFA. Incidence of ventricular premature beats (VPBs) was expressed on a histogram by the number for every one minute (a part of the trend chart automatically analysed by DYNAGRAM Model DCG-6000).

A: VPBs occurred only in a early phase after coronary ligation and supplement of excess FFA increased the incidence of VPBs (Case 2).

B: The incidence of VPBs gradually increased up to 60 minutes after coronary ligation and subsided thereafter. Supplement of excess FFA slightly increased the incidence (Case 1).

C: The occurrence of VPBs continued up to 80 minutes after coronary ligation. The incidence of VPBs was not increased by excess FFA (Case 3).

duration was too long for L-carnitine to effect the significant improvement in the tissue levels of metabolites.

Since high levels of long chain acyl CoA inhibits adenine nucleotide translocase<sup>32</sup> that is the regulator of the egression of ATP across the inner mitochondrial membrane, accumulation of long chain acyl CoA is supposed to exaggerate the depleted ATP production by reduced oxygen supply in ischemic myocardium. And the ratio of long chain acyl CoA to free carnitine was suggested to be important in regulating the activity of several enzymes during early phases of ischemia.<sup>19</sup> However, in these periods, the increase in long chain acyl carnitine was nearly three times of the increase in long chain acyl CoA.<sup>31,33,34</sup> In

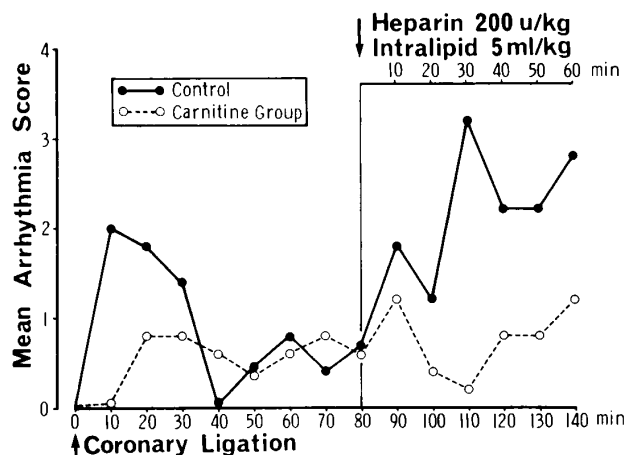


Fig.6. Effect of L-carnitine on excess FFA induced arrhythmias. Effect of L-carnitine on excess FFA induced arrhythmias was evaluated in the cases in which every score in a period from 40 to 80 minutes of coronary occlusion was below 2. Pretreatment of L-carnitine prevented the aggravation of the grade of ventricular arrhythmias induced by excess FFA. Control = Case 2, 10, 12, 16, 18. Carnitine group = Case 7, 9, 11, 13, 21.

addition, negative correlation was observed not only between ATP and the ratio of long chain acyl CoA to free carnitine, but also between ATP and the ratio of long chain acyl carnitine to free carnitine.<sup>31</sup> And the effect of L-carnitine was more prominent in the reduction in long chain acyl carnitine than that in long chain acyl CoA.<sup>31</sup> It has been also reported that long chain acyl carnitine is a more powerful inhibitor of the activity of bovine heart  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase than long chain acyl CoA,<sup>35</sup> and it is also an inhibitor of the  $\text{Ca}^{++}$ -ATPase activity of cardiac sarcoplasmic reticulum isolated from dog hearts.<sup>36</sup> Serious ventricular arrhythmias in early phase following coronary occlusion were prevented by the pretreatment of L-carnitine. And in this study, ventricular fibrillation occurred only in a case of the controls. Taken together with the results of our previous studies<sup>21,31</sup> 8 of 52 untreated dogs (15.4%) manifested ventricular fibrillation, whereas only one of 26 dogs treated with L-carnitine (3.4%) had fibrillation 5 to 15 minutes after coronary occlusion. From these observations, accumulation of long chain acyl carnitine appears to be one of the factors that cause ventricular arrhythmias in ischemic heart.

#### Ventricular arrhythmias induced by excess FFA

When excess FFA was supplemented in cases

in which ventricular arrhythmias subsided 40 to 80 minutes after coronary occlusion, the grade of ventricular arrhythmias increased again. Pretreatment of L-carnitine reduced the grade of these arrhythmias and tended to reduce the increased tissue long chain acyl carnitine levels.

Arrhythmogenic effect of high plasma FFA in acute myocardial infarction has been reported in man<sup>1</sup> and animals<sup>2,3</sup> and several explanations have been proposed as the mechanisms<sup>4-11</sup>. However those results could not be repeated by other investigators<sup>37,38</sup>. Although the difference has been explained that arrhythmogenic effect was due not to the absolute level of FFA but rather to the FFA/albumin molar ratio<sup>3</sup>, the results in this study suggest that the accumulated long chain acyl carnitine may also play an important role in the genesis of the ventricular arrhythmias induced by excess FFA, as well as coronary artery occlusion. In other words, whether excess FFA are able to provoke arrhythmias or not may be due not only to FFA/albumin molar ratio, but also to the tissue carnitine concentrations that is essential for the oxidation of long chain fatty acyl derivatives.

From this point of view, administration of L-carnitine is supposed to be beneficial to prevent serious arrhythmias in ischemic heart disease, presumably by restoring the impaired FFA oxidation.

#### Acknowledgement

We are grateful for the technical assistance of Mr. S. Uenoyama, Mr. K. Takahashi and Mr. K. Tsutsumi in Otsuka Pharmaceutical Factory Inc.

#### REFERENCES

1. OLIVER MF, KURIEN VA, GREENWOOD TW: Relation between serum free fatty acids and arrhythmias and death after acute myocardial infarction. *Lancet* 1: 710, 1968
2. 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
3. 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, 1971
4. KURIEN VA, OLIVER MF: A metabolic cause for arrhythmias during acute myocardial hypoxia. *Lancet* 1: 813, 1970
5. WASILEWSKA-DZIUBINSKA E, CZARNECKA M, BERESWICZ A, LEWARTOWSKI B: Influence of sodium palmitate on the cellular action potentials of the left ventricle of isolated perfused guinea-pig heart. *Acta Physiol Pol* 26: 1, 1975
6. COWAN JC, VAUGHAN WILLIAMS EM: The effects of palmitate on intracellular potentials recorded from Langendorff-perfused guinea-pig hearts in normoxia and hypoxia and during perfusion at reduced rate of flow. *J Mol Cell Cardiol* 9: 327, 1977
7. RAVENS KG, RAVENS U: The role of linoleic acid in hypoxia-induced changes of the action potentials and the force of contraction of isolated papillary muscles of the guinea pig. In *Recent Advances in Studies on Cardiac Structure and Metabolism*, Vol 7: Biochemistry and Pharmacology of Myocardial Hypertrophy, Hypoxia and Infarction, ed by Harris P, Bing RJ, Fleckenstein A, University Park Press, Baltimore, 1976, p 289
8. BORST P, LOOS JA, CHRIST EJ, SLATER EC: Uncoupling activity of long chain fatty acids. *Biochim Biophys Acta* 62: 509, 1962
9. LOCHNER A, KOTZE JCN, GEVERS W: Mitochondrial oxidative phosphorylation in myocardial anoxia. Effects of albumin. *J Mol Cell Cardiol* 8: 465, 1976
10. YAMAZAKI, SUZUKI Y, KAMIKAWA T, OGAWA K, MIZUTANI K, KAKIZAWA N, YAMAMOTO M: Arrhythmogenic effects of acute free fatty acid mobilization on ischemic heart. In *Recent Advances in Studies on Cardiac Structure and Metabolism*, Vol 12: Cardiac Adaptation, ed by Kobayashi T, Ito Y, Rona G, University Park Press, Baltimore, 1978, p271
11. KATO T, SUZUKI S, KAMBE T, SAKAMOTO N, SUGIYAMA S, OZAWA T: Arrhythmogenic effect of free fatty acids in relation to heart mitochondrial function. *J Appl Biochem* 1: 139, 1979
12. SHUG AL, SHRAGO E, BITTAR N, FOLTS JD, KOKE JR: Acyl-CoA inhibition of adenine nucleotide translocation in ischemic myocardium. *Am J Physiol* 228: 689, 1975
13. SHRAGO E, SHUG AL, SUL H, BITTAR N, FOLTS JD: Control of energy production in myocardial ischemia. *Circ Res* 38 (Suppl 1): 75, 1976
14. LIEDTKE AJ, NELLIS S, NEELY JR: Effects of excess free fatty acids on mechanical and metabolic function in normal and ischemic myocardium in swine. *Circ Res* 43: 652, 1978
15. OPIE LH: Role of carnitine in fatty acid metabolism of normal and ischemic myocardium. *Am Heart J* 97: 375, 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. SCHWARTZ A, WOOD JM, ALLEN JC, BORNET EP, ENTMAN ML, GOLDSTEIN MA, SORDAHL LA, SUZUKI M, LEWIS ML: Biochemical and morphologic correlates of cardiac ischemia. I. Membrane systems. *Am J Cardiol* 32: 46, 1973
19. 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
20. 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
21. SUZUKI Y, KAMIKAWA T, YAMAZAKI N: Protective effects of L-carnitine on ischemic heart. In *Carnitine Biosynthesis, Metabolism, and Functions*, ed by Frenkel RA, MacGarry JD, Academic Press, New York, 1980, p341
  22. FOLTS JD, SHUG AL, KOKE JR, BITTAR N: Protection of the ischemic dog myocardium with carnitine. *Am J Cardiol* **41**: 1209, 1978
  23. LIEDTKE AJ, NELLIS SH: Effects of carnitine in ischemic and fatty acid supplemented swine hearts. *J Clin Invest* **64**: 440, 1979
  24. MARQUIS NR, FRITZ IB: Enzymological determination of free carnitine concentrations in rat tissues. *J Lipid Res* **5**: 184, 1964
  25. PEARSON DJ, CHASE JFA, TUBBS PK: The assay of (-)-carnitine and its o-acyl derivatives. *Methods in Enzymology* **14**: 612, 1969
  26. LAMPRECHT W, TRAUTSCHOLD I: Adenosine-5'-triphosphate: Determination with hexokinase and glucose-6-phosphate dehydrogenase. *Methods of Enzymatic Analysis* **4**: 2101, 1975
  27. ITAYA K, UI M: Colorimetric determination of free fatty acids in biological fluids. *J Lipid Res* **6**: 16, 1965
  28. LOWN B, WOLF M: Approaches to sudden death from coronary heart disease. *Circulation* **44**: 130, 1971
  29. WIT AL, BIGGER JT: Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. *Circ Res* **51-52** (Suppl 3): 96, 1975
  30. OPIE LH, NATHAN D, LUBBE WF: Biochemical aspects of arrhythmogenesis and ventricular fibrillation. *Am J Cardiol* **43**: 131, 1979
  31. SUZUKI Y, KAMIKAWA T, KOBAYASHI A, MASUMURA Y, YAMAZAKI N: Effects of L-carnitine on tissue levels of acyl carnitine, acyl CoA and high energy phosphate in ischemic dog hearts. *Jpn Circul J* (in press)
  32. 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
  33. ORAM JF, BENNTCH SL, NEELY JR: Regulation of fatty acid utilization in isolated perfused rat hearts. *J Biol Chem* **248**: 5299, 1973
  34. NEELY JR, ROVETTO MJ, WHITMER JT: Rate-limiting steps of carbohydrate and fatty acid metabolism in ischemic hearts. *Acta Med Scand (Suppl)* **587**: 9, 1976
  35. WOOD JM, BUSH B, PITTS BJR, SCHWARTZ A: Inhibition of bovine heart  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase by palmitylcarnitine and palmityl-CoA. *Biochem Biophys Res Commun* **74**: 677, 1977
  36. PITTS BJR, TATE CA, VON WINKLE WB, WOOD JM, ENTMAN ML: Palmitylcarnitine inhibition of calcium pump in sarcoplasmic reticulum: A possible role in myocardial ischemia. *Life Sci* **23**: 391, 1978
  37. OPIE LH, NORRIS RN, THOMAS M, HOLLAND AJ, OWEN P, VAN NOORDEN S: Failure of high concentrations of circulating free fatty acids to provoke arrhythmias in experimental myocardial infarction. *Lancet* **1**: 818, 1971
  38. KOSTIS JB, MAVROGEORGIS EA, HORSTMANN E, GORZOYANNIS S: Effect of high concentrations of free fatty acids on the ventricular fibrillation threshold of normal dogs and dogs with acute myocardial infarction. *Cardiology* **58**: 89, 1973