Z. Kardiol. 76, Supplement 5 (1987)

E. Fleck, V. Regitz, A. L. Shug (eds.)

Carnitine metabolism

Role in acute ischemia and chronic myocardial disease

Carnitinstoffwechsel

Bedeutung für akute Ischämie und chronische Myokarderkrankungen

Steinkopff Verlag Darmstadt

Zeitschrift für
Kardiologie

Z. Kardiol. 76: Suppl. 5, 14 – 18 (1987)

The effect of preoperative L-carnitine supplementation on myocardial metabolism during aorto-coronary bypass surgery

H. Böhles*, Th. Noppeney**, Z. Akcetin*, J. Rein**, J. von der Emde**

University of Erlangen, *Department of Pediatrics; ** Department of Cardiac Surgery, F.R.G.

Wirkung präoperativer L-Carnitin-Substitution auf den Myokardstoffwechsel während aorto-koronarer Bypassoperation

Zusammenfassung: Ischämiebedingte Veränderungen des Myokardstoffwechsels sind durch einen frühzeitigen Anstieg langkettiger Fettsäure-Coenzym-A-Ester charakterisiert. Langkettige Fettsäure-Coenzym-A-Ester inhibieren den Adeninnukleotidtranslokator und so den Austausch zwischen mitochondrialem und zytoplasmatischem ATP und ADP, hemmen weitere Schlüsselenzyme der Zelle und schädigen Membranen durch ihre Wirkung als Detergentien. Ihre Akkumulation und, in der Folge, die der entsprechenden Carnitinester stellt einen wesentlichen Faktor in der Pathogenese der ischämischen Zellschädigung dar. Die Zufuhr freien Carnitins bei Ischämie soll die Konzentrationen dieser toxischen Metabolite reduzieren und zu einer Verbesserung des Energiestoffwechsels beitragen.

Die Wirkung von Carnitin auf den myokardialen Energiestoffwechsel wurde an Patienten mit definierter Myokardischämie während aortokoronarer Bypassoperation untersucht. 68 Patienten wurden präoperativ entweder zu einer L-Carnitin behandelten Gruppe (n = 41) oder zu einer Kontrollgruppe (n = 20) randomisiert. Die Therapiegruppe erhielt L-Carnitin, 1 g/Tag p.o., 2 Tage präoperativ und 0,5 g L-Carnitin i.v. unmittelbar präoperativ. Intraoperativ wurde bei der Kanülierung des rechten Vorhofs für die extrakorporale Zirkulation die Spitze des rechten Vorhofohrs für die Bestimmung von ATP, Lactat, freiem Carnitin und der Carnitinester entnommen.

Myokardiale ATP-Konzentrationen in der carnitinsubstituierten Gruppe lagen signifikant über denen einer Kontrollgruppe (Abb. 2), und es fand sich eine inverse Korrelation zwischen myokardialen ATP- und Laktatkonzentrationen (Abb. 3). Dabei lagen in der carnitinbehandelten Gruppe das freie Carnitin im Myokard signifikant über und die langkettigen Carnitinester signifikant unter den Spiegeln der Kontrollgruppe, ohne daß die Gesamtcarnitinspiegel in beiden Gruppen differierten (Abb. 1). Der postoperative Bedarf an positiv inotroper Medikation war in der carnitinbehandelten Gruppe auf weniger als die Hälfte der Kontrollgruppe reduziert. Sonst unterschieden sich die beiden Patientengruppen in Bezug auf klinische Daten und Laborparameter im peri- und unmittelbar postoperativen Verlauf nicht voneinander. Wir postulieren, daß eine L-Carnitin-Substitution während aortokoronarer Bypassoperation zur Normalisierung des myokardialen Energiestoffwechsels beitragen kann.

Schlüsselwörter: Myokardstoffwechsel; aortokoronare Bypassoperation; Carnitin.

Summary: 68 patients with defined myocardial ischemia, undergoing aorto-coronary bypass operation were assigned either to a group supplemented with L-carnitine (n = 41) or to a control group (n = 27). When extracorporeal circulation was established, a small piece of the right atrial appendage was biopsied and prepared for analysis for ATP, lactate and carnitine fractions. The ATP concentrations were higher in the patients supplemented with carnitine. A negative correlation existed between ATP and lactate levels. The amount of total carnitine was similar in both groups. However, free carnitine was higher, and long-chain acylcarnitine was lower when L-carnitine was supplemented. Postoperatively, the patients needed less inotropic medicaments, when supplemented with L-carnitine. L-carnitine supplementation in patients needed less inotropic medicaments, when supplemented with L-carnitine. L-carnitine supplementation in patients undergoing

aorto-coronary bypass operation proved to be effective and beneficial for the normalization of myocardial energy metabolism parameters.

Key words: aorto-coronary bypass surgery; L-carnitine supplementation; myocardial energy metabolism.

The normal myocardium derives most of its energy from the oxidation of fatty acids (1), but this process declines sharply in myocardial ischemia. This inhibition of the energy metabolism of fatty acids is based on inhibition of the intramitochondrial β-oxidation, due to a reduction in the activity of carnitine acyltransferase I (2). As a result, the intracellular concentration of long-chain fatty acid acyl-CoA esters increases (3), and when this concentration reaches a critical level, adenine nucleotide translocase – the enzyme that catalyzes the exchange of ATP and ADP between the mitochondria and cytoplasm (4) – as well as Na^+-K^+-ATPase (5), are inhibited. The disruption of these important transport processes leads to a reduction in cytoplasmic ATP concentrations and is thought to exaggerate myocardial ischemic damage. Also, long-chain acylcarnitine conjugates are increased in the ischemic heart muscle and exert a detergent effect on the cellular membrane. The effect is a further inhibition of the Ca-ATPase, Na^+-K^+-ATPase and adenine nucleotide translocase activities. Therefore it should be stressed that the accumulation of activated long chain fatty acids, as well as of long chain acylcarnitines represents a major factor in the pathogenesis of ischemic heart disease. From animal studies, it has been reported that replacement of carnitine alleviates the accumulation of long chain acylcarnitines and results in the improvement of energy metabolism and mechanical performance (6).

The present study was designed to investigate whether carnitine, administered preoperatively, improves the metabolic changes of ischemically compromised heart muscle in patients undergoing aorto-coronary-bypass surgery.

Patients and Methods

68 patients scheduled for aorto-coronary bypass (ACB) operation (63 men, five women) as a consequence of ischemic heart disease, were randomly assigned to a group supplemented with L-carnitine (n = 41; 39 men, two women; mean age: 57.4 ± 7 years; mean weight 75.6 ± 8 kg) and a control group (n = 27; 24 men, three women; mean age: 57.3 ± 6 years; mean weight: 75.9 ± 7 kg). The carnitine supplemented group received 1 g L-carnitine per day orally, divided into three equal doses for 2 days prior to the operation, and 0.5 g L-carnitine intravenously immediately before the operation, when anesthesia was started. During the operation, when the right atrial appendage (RAA) was cannulated to establish extracorporal circulation, the tip of the RAA (about 100 mg) was biopsied and immediately placed in liquid nitrogen.

The tissues were stored at −75 °C until analysis. At the end of the operation, a blood sample was preserved for determination of the serum carnitine concentration. In a retrospective analysis, clinical and chemical postoperative parameters were taken from the patients' charts in the intensive care unit, when the patients were observed postoperatively. The parameters were recorded upon arrival at the intensive care unit (ICU) and at 8 a.m. on the first postoperative day.

Of the 68 patients, we formed a statistical analysis of 20 pairs of patients comparable in age, sex, amount of venous grafts received, and time spent on the heart-lung machine during the operation (Table 1). One patient from each pair was supplemented with L-carnitine, whereas the other was not. In 43 of the 68 heart tissue specimens, we were also able to analyse ATP and lactate levels. Among these 43 specimen's, 38 belonged to patients grouped for paired analysis.

Carnitine and its fractions were determined according to McGarry and Foster (7) in a 5 % perchloric acid homogenate of the heart muscle. ATP was determined by enzyme assay using hexokinase and glucose-6-phosphate dehydrogenase. Lactate was assayed enzymatically with a commercially available system (Boehringer Mannheim). The values are reported relative to wet weight as means ± 1 SD.

Statistical analysis of the data was performed with the Mann-Whitney U test and Wilcoxon's test for paired differences.

Results

The total carnitine concentrations in the heart muscle of both groups were not significantly different. However, myocardial free carnitine had increased and long-chain acylcarnitine had decreased significantly when carnitine was supplemented (Fig. 1). The same values were similar when calculated in the 40 patients grouped for paired analysis. The postoperative serum carnitine concentrations showed a large scatter. However, the concentrations of total carnitine were significantly higher in supplemented patients (38.7 ± 16 nmol/ml; 71.8 % free carnitine) when compared with unsupplemented patients (20.3 ± 7 nmol/ml; 61.6 % free carnitine) ($p < 0.05$).

The myocardial ATP concentrations in the patients given carnitine were significantly higher than in the unsupplemented group (Fig. 2). When the myocardial ATP concentrations are plotted against the heart muscle lactate concentrations, it appears obvious that higher ATP values correspond to lower amounts of lactate and vice versa (Fig. 3).

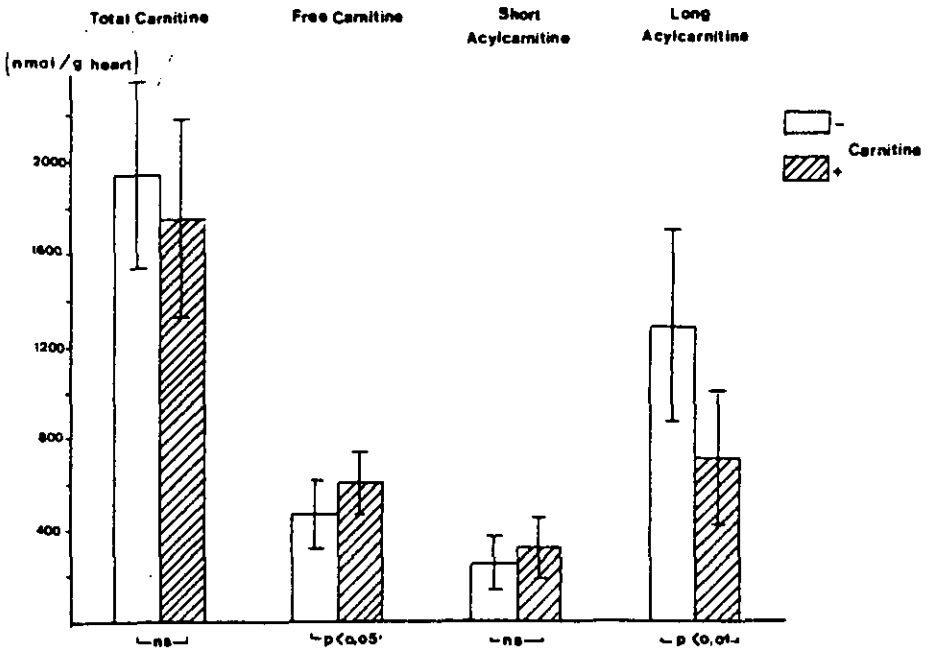

Fig. 1. Concentrations of carnitine fractions in the right atrial appendage of patients undergoing aorto-coronary bypass operation (Supplemented with carnitine $n = 41$. controls $n = 27$).

The results of the paired analysis of clinical and chemical data are listed in Table 1. The parameters were not different between the two groups except for the amounts of inotropic medicaments needed. The carnitine-supplemented patients needed less than half the amount of these than those in the control group.

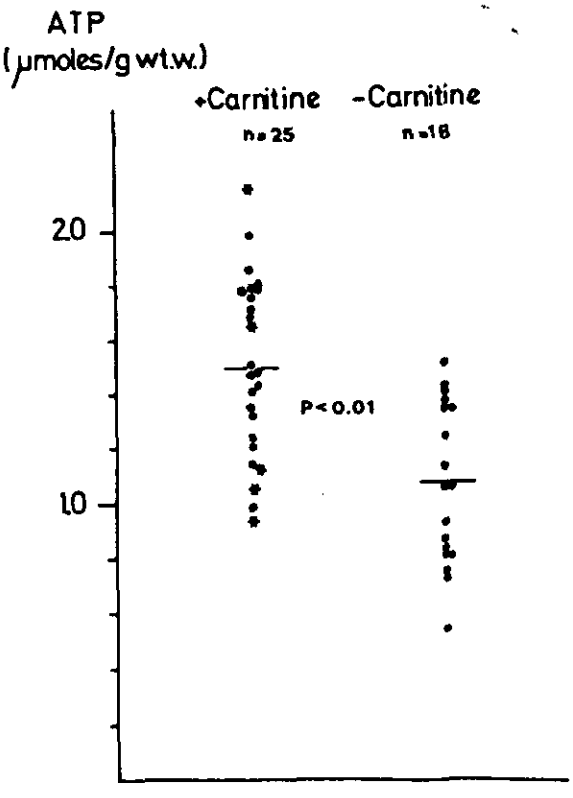

Fig. 2. ATP concentrations in the right atrial appendage of patients undergoing aorto-coronary bypass operation. * patients not belonging to the 40 patients grouped for paired analysis.

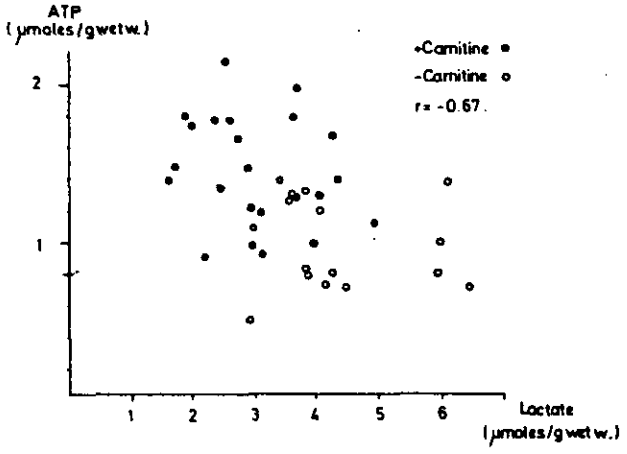

Fig. 3. Relationship between ATP and lactate concentrations in the right atrial appendage of patients undergoing aortocoronary bypass operation.

Discussion

Recently, considerable attention has been focused on the role of carnitine in impaired fatty acid metabolism in ischemic myocardium (8–10). It has been ascertained that anoxia or even ischemia cause an accumulation of long-chain fatty acids and their metabolites, in particular acyl-CoA and long-chain acylcarnitine (11), with a concomitant decrease of free carnitine. This is due either to its leakage from the tissue or to its esterification to acylcarnitine. The idea of an increased loss from the myocardial cells may be supported by our analysis of 70 post mortem hearts. Those patients dying from severe heart disease (mostly ischemic heart disease) had lower total myocardial carnitine concentrations than those dying from other causes (Fig. 4). Aorto-coronary bypass operation was performed in 68 patients after ischemic coronary heart disease had been proved by selective coronary an-

Table 1. Preoperative and postoperative clinical and chemical parameters of 40 patients undergoing aorto-coronary bypass operation.

	Supplemented Carnitine (n = 20)	Control Group (n = 20)	*P* Value
Age	57.3 ± 8.7	57.0 ± 7.7	NS
Duration of bypass (min)	65.1 ± 16.9	66.3 ± 12.6	NS
Duration of hypothermia (min)	41.2 ± 17.5	36.5 ± 15.3	NS
Intraoperative pH	7.34 ± 0.42	7.36 ± 0.47	NS
Urine volume during operation	1403 ± 505	1477 ± 650	NS
Arrival at ICU			
RR syst. (mmHg)	116 ± 13	119 ± 15	NS
RR dist. (mmHg)	73 ± 12	73 ± 9	NS
Beats/min	89 ± 15	89 ± 13	NS
Central venous pressure	9.1 ± 4.3	10.3 ± 4.5	NS
Hemoglobin (gm/dl)	12.0 ± 0.8	12.4 ± 1.1	NS
pH	7.42 ± 0.4	7.42 ± 0.4	NS
Base excess (mEq/L)	− 1.65 ± 1.7	− 1.64 ± 5.3	NS
Na (mEq/L)	130 ± 5.1	133 ± 5.5	NS
K (mEq/L)	4.3 ± 0.6	4.1 ± 0.6	NS
Day 1, 8 $_{AM}$			
RR syst. (mmHg)	119 ± 9	127 ± 15	NS
RR diast. (mmHg)	75 ± 8	76 ± 11	NS
Beats/min	84 ± 14	86 ± 13	NS
Central venous pressure	8.5 ± 3.6	10.6 ± 3.7	NS
Blood glucose (mg/dl)	176 ± 55	173 ± 55	NS
Creatinine (mg/dl)	1.2 ± 0.2	1.2 ± 0.2	NS
Extubation (h postop)	8.0 ± 1.6	9.0 ± 3.3	NS
Dopamine (mg/kg)	0.132 ± 0.42	0.374 ± 1.23	<0.01
Dobutamine (mg/kg)	0.165 ± 0.52	0.454 ± 1.57	<0.01
Glyceroltrinitrate (mg/kg)	0.580 ± 0.76	0.937 ± 1.01	<0.02

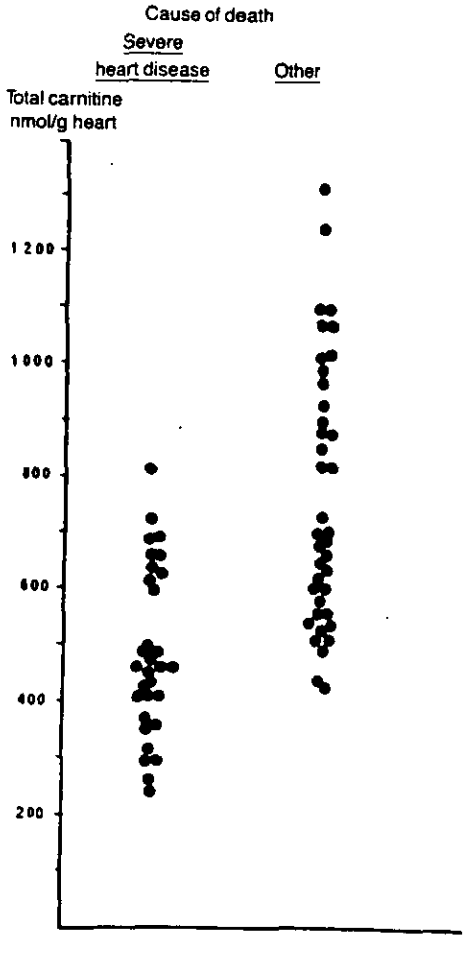

Fig. 4. Total myocardial carnitine concentrations from 70 autopsy examinations grouped according to cause of death.

giography. The effect of oral carnitine supplementation on myocardial metabolites agrees with the results obtained in animal experiments (12), in which the effect of carnitine on ischemic myocardium was tested. Pretreatment with L-carnitine prevented the decrease in free carnitine and the increase in long-chain acylcarnitine. The significance of this effect is expressed as higher ATP concentrations when carnitine is supplemented, because the function of essential enzymatic activities may be reestablished.

The lower myocardial lactate concentrations corresponding to higher ATP values may reflect the hemodynamic action of carnitine, resulting in better tissue oxygenation (13). The lowering of lactate concentrations also may be explained if one considers that ischemia causes an accumulation of long-chain acyl-CoA with an increase of the acyl-CoA/CoA ratio. This inhibitis the activity of pyruvate dehydrogenase, the enzyme which regulates the entry of pyruvate into the citric acid cycle. Under these conditions, pyruvate is converted to lactate. L-carnitine may reduce lactate production either by activating pyruvate dehydrogenase directly or by provoking a decrease in the acyl-CoA/CoA ratio as a consequence of acyl removal from CoA (14) (Fig. 5).

Our analysis of clinical and chemical data taken postoperatively from the charts of patients in ICU show that patients given carnitine needed significantly less catecholamines than controls. This aspect fits into the described chemical cellular alterations.

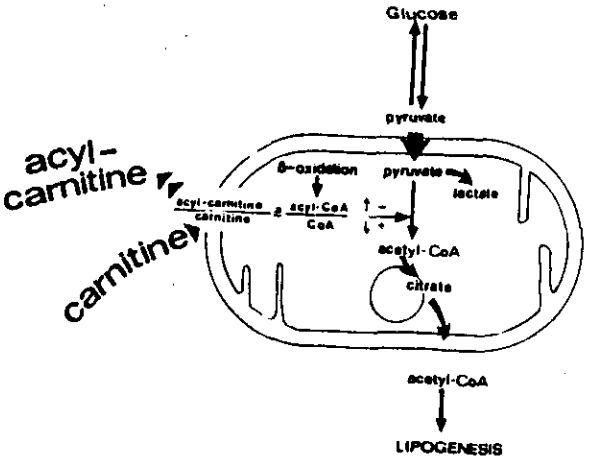

Fig. 5. Hypothetical effect of carnitine on the regulation of pyruvate dehydrogenase activity.

However, it should be interpreted with care, because the use of catecholamines is a very subjective decision made by the physician on duty. Preoperative L-carnitine supplementation in patients undergoing aorto-coronary bypass surgery proved to be effective and beneficial with respect to the normalization myocardial energy metabolism parameters.

References

1. Neely JR, Rovetto MJ, Oram JF (1972) Myocardial utilization of carbohydrates and lipids. Prog Cardiovasc Disc 15: 289–329
2. Wood JM, Sordahl LA, Lewis RM (1973) Effect of chronic myocardial ischemia on the activity of carnitine palmityl conenzyme A transferase of isolated canine heart mitochondria. Circ Res 32: 340–347
3. Shrago E, Shug AL, Sul H (1975) Control of energy production in myocardial ischemia. Circ Res 38: Suppl I: I–75–179
4. Ho CH, Pande SV (1974) On the specificity of the inhibition of adenine nucleotide translocase by long-chain acyl coenzyme A esters. Biochim Biophys Acta 369: 86–92
5. Lamers JMJ, Hülsmann WC (1977) Inhibition of (Na K)-stimulated ATPase of heart by fatty acids. J Mol Cell Cardiol 9: 343
6. Suzuki Y, Kamikawa T, Kobayashi A (1981) Effects of L-carnitine on tissue levels of acylcarnitine acyl-CoA and high energy phosphate in ischemic dog hearts. Jpn Circ J 45: 687
7. McGarry JD, Foster DW (1976) An improved and simplified radioisotopic assay for the determination of free and esterified carnitine. J Lipid Res 17: 277
8. Shug AL, Thomsen JH, Folts JD (1978) Changes in tissue levels of carnitine and other metabolites during myocardial ischemia and anoxia. Arch Biochem Biophys 187: 25
9. Whitmer JT, Idell-Wenger JA, Rovetto MJ, Neely JR (1978) Control of fatty acid metabolism in ischemic and hypoxic heart. J Biol Chem 253: 4305
10. Folts JD, Shug AL, Koke JR, Bittar N (1978) Protection of ischemic myocardium with carnitine. Am J Cardiol 41: 1209
11. Liedke AJ (1981) Alterations of carbohydrate and lipid metabolism in the acute ischemic heart. Prog Cardiovasc Dis 23: 321
12. Paulson DJ, Shug AL (1982) Effects of carnitine on the ischemic arrested heart. Basic Res Cardiol 77: 460
13. Brooks H, Goldberg L, Holland R (1977) Carnitine-induced effects on cardia and peripheral hemodynamics. J Clin Pharmacol 17: 561
14. Ferrari R, Cucchini F, Visioli O (1984) The metabolic effects of L-carnitine in angina pectoris. Int J Cardiol 5: 213

Authors' address:
Prof. Dr. H. Böhles
Universitätskinderklinik
Loschgestraße 15
8520 Erlangen
F.R.G.

CURRENT
THERAPEUTIC
RESEARCH
VOL. 39, NO. 3, MARCH 1986

THE EFFECT OF PREOPERATIVE L-CARNITINE SUPPLEMENTATION ON MYOCARDIAL METABOLISM DURING AORTO-CORONARY-BYPASS SURGERY

H. BÖHLES,* Th. NOPPENEY,** Z. AKCETIN,* J. REIN,** AND J. VON DER EMDE**

*University of Erlangen, Department of Pediatrics, **University of Erlangen, Department of Cardiac Surgery, Erlangen, Federal Republic of Germany

ABSTRACT

Sixty-eight patients undergoing aorto-coronary bypass operation were assigned to a group supplemented with L-carnitine (n = 41) or a control group (n = 27). When extracorporal circulation was established, a small piece of the right atrial appendage was biopsied and prepared for analysis of ATP, lactate, and carnitine fractions. The ATP concentrations were higher in the patients supplemented with carnitine. A negative correlation existed between ATP and lactate levels. The amount of total carnitine was similar in both groups. However, free carnitine was higher, and long-chain acylcarnitine was lower when L-carnitine was supplemented. L-carnitine supplementation in patients undergoing aorto-coronary bypass operation proved to be effective and beneficial for the normalization of parameters of myocardial energy metabolism.

INTRODUCTION

Myocardial fatty acid metabolism depends on carnitine as an essential cofactor. While the total tissue carnitine level remains constant in the normal heart, it can be altered under various pathological conditions. A reduction in free carnitine and an accumulation of long-chain acylcarnitine have been demonstrated in ischemic myocardium.[1] Long-chain acylcarnitine has been reported to inhibit adenine nucleotide transferase,[2] the carnitine-palmityl CoA transferase,[3] as well as $Na^+,K^+-ATPase$.[4] These alterations are thought to exaggerate myocardial ischemic damage.[5] In animal experiments it was reported that replacement of carnitine alleviates the accumulation of long-chain acylcarnitine and results in the improvement of energy metabolism and mechanical performance.[6] The present study was designed to investigate whether carnitine administered preoperatively improves the metabolic changes of ischemically compromised heart muscle in patients undergoing aorto-coronary bypass surgery.

Address reprint requests to: Prof. Dr. H. Böhles, Universitätskinderklinik, Loschgestrasse 15, 8520 Erlangen, Federal Republic of Germany

0011-393X/86/$3.50

PATIENTS AND METHODS

Sixty-eight patients scheduled for aorto-coronary bypass operation (63 men, five women) as a consequence of ischemic heart disease were randomly assigned to a group supplemented with L-carnitine (n = 41: 39 men, two women; mean age, 57. 4 ± 7 years; mean weight, 75. 6 ± 8 kg) and a control group (n = 27: 24 men, three women; mean age, 57.3 ± 6 years; mean weight, 75.9 ± 7 kg). The carnitine-supplemented group received 1 gm of L-carnitine per day orally, divided into three equal doses for two days prior to the operation, and 0.5 gm of L-carnitine intravenously immediately before the operation, when anesthesia was started. During the operation, when the right atrial appendage (raa) was cannulated to establish extracorporal circulation, the tip of the raa (about 100 mg) was biopsied and placed immediately in liquid nitrogen. Until analysis the tissues were stored at −75°C. At the end of the operation, a blood sample was preserved for determination of the serum carnitine concentration. In a retrospective analysis, clinical and chemical postoperative parameters were taken from the charts of patients in the intensive care unit, where the patients were observed postoperatively. The parameters were recorded upon arrival at the intensive care unit (ICU) and at 8 AM on the first postoperative day.

Of the 68 patients, we formed a statistical analysis for 20 pairs of patients comparable in age, sex, amount of venous grafts received, and time spent on the heart-lung machine during the operation (Table). One patient of a pair was supplemented with L-carnitine whereas the other was not. In 43 of the 68 heart tissue specimens, we were also able to analyze ATP and

Table I. Preoperative and postoperative clinical and chemical parameters of 40 patients undergoing aorto-coronary bypass.

	Supplemented Carnitine (n = 20)	Control Group (n = 20)	P Value
Age	57.3 ± 8.7	57.0 ± 7.7	NS
Duration of bypass (min)	65.1 ± 16.9	66.3 ± 12.6	NS
Duration of hypothermia (min)	41.2 ± 17.5	36.5 ± 15.3	NS
Intraoperative pH	7.34 ± 0.42	7.36 ± 0.47	NS
Urine volume during operation	1403 ± 505	1477 ± 650	NS
Arrival at ICU			
Resting rate systolic (mmHg)	116 ± 13	119 ± 15	NS
Resting rate diastolic (mmHg)	73 ± 12	73 ± 9	NS
Beats/min	89 ± 15	89 ± 13	NS
Central venous pressure	9.1 ± 4.3	10.3 ± 4.5	NS
Hemoglobin (gm/dl)	12.0 ± 0.8	12.4 ± 1.1	NS
pH	7.42 ± 0.4	7.42 ± 0.4	NS
Base excess (mEq/L)	−1.65 ± 1.7	−1.64 ± 5.3	NS
Na (mEq/L)	130 ± 5.1	133 ± 5.5	NS
K (mEq/L)	4.3 ± 0.6	4.1 ± 0.6	NS
Day 1, 8 AM			
Resting rate systolic (mmHg)	119 ± 9	127 ± 15	NS
Resting rate diastolic (mmHg)	75 ± 8	76 ± 11	NS
Beats/min	84 ± 14	86 ± 13	NS
Central venous pressure	8.5 ± 3.6	10.6 ± 3.7	NS
Blood glucose (mg/dl)	176 ± 55	173 ± 55	NS
Creatinine (mg/dl)	1.2 ± 0.2	1.2 ± 0.2	NS
Extubation (hrs postop)	8.0 ± 1.6	9.0 ± 3.3	NS
Dopamine (mg/kg)	0.132 ± 0.42	0.374 ± 1.23	<0.01
Dobutamine (mg/kg)	0.165 ± 0.52	0.454 ± 1.57	<0.01
Glyceroltrinitrate (mg/kg)	0.580 ± 0.76	0.937 ± 1.01	<0.02

lactate levels. Among these 43 specimens, 38 belonged to patients grouped for paired analysis.

Carnitine and its fractions were determined according to McGarry and Foster[7] in a 5% perchloric acid homogenate of the heart muscle. ATP was determined by enzyme assay using hexokinase and glucose-6-phosphate dehydrogenase.[8] Lactate was assayed enzymatically with a commercially available system (Boehringer Mannheim). The values are reported relative to wet weight as mean ± 1 SD.

Statistical analysis of the data was performed with the Mann-Whitney U test and Wilcoxon's test for paired differences.

RESULTS

The total carnitine concentrations in the heart muscle of both groups were not significantly different. However, myocardial free carnitine had increased and long-chain acylcarnitine had decreased significantly when carnitine was supplemented (Figure 1). The same values were similar when calculated in the 40 patients grouped for paired analysis.

The postoperative serum carnitine concentrations showed a large scatter. However, the concentrations of total carnitine were significantly higher in supplemented patients (38.7 ± 16 nmol/ml; 71.8% free carni-

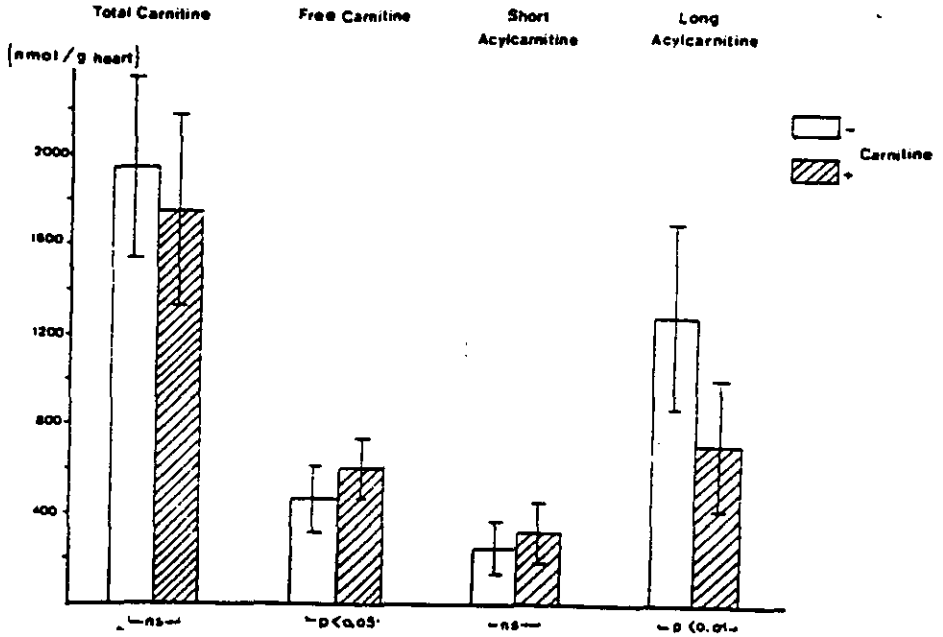

Figure 1. Concentrations of carnitine fractions in the right atrial appendage of patients undergoing aorto-coronary bypass operation. (Supplemented with carnitine: n = 41; controls: n = 27)

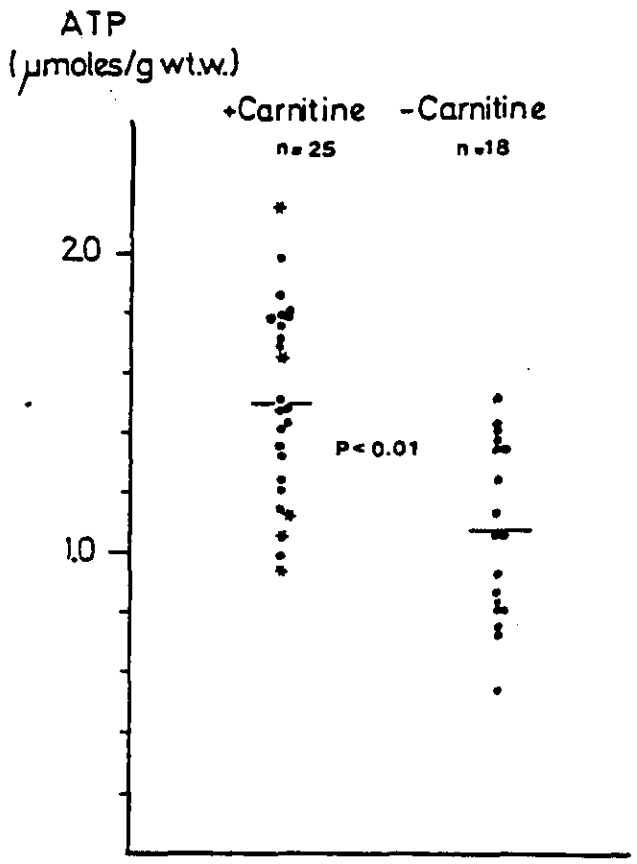

Figure 2. ATP concentrations in the right atrial appendage of patients undergoing aorto-coronary bypass operation. * = patients not belonging to the 40 patients grouped for paired analysis.

tine) when compared with unsupplemented patients (20.3 ± 7 nmol/ml; 61.6% free carnitine) ($P < 0.05$).

The myocardial ATP concentrations in the patients given carnitine were significantly higher than in the unsupplemented group (Figure 2). When the myocardial ATP concentrations were plotted against the heart muscle lactate concentrations, it appears obvious that higher ATP values correspond to lower amounts of lactate and vice versa (Figure 3).

The results of the paired analysis of clinical and chemical data are listed in the Table. The parameters were not different between the two groups except for the amounts of inotropic medicaments needed. The carnitine-supplemented patients had received less than half the amount than those in the control group.

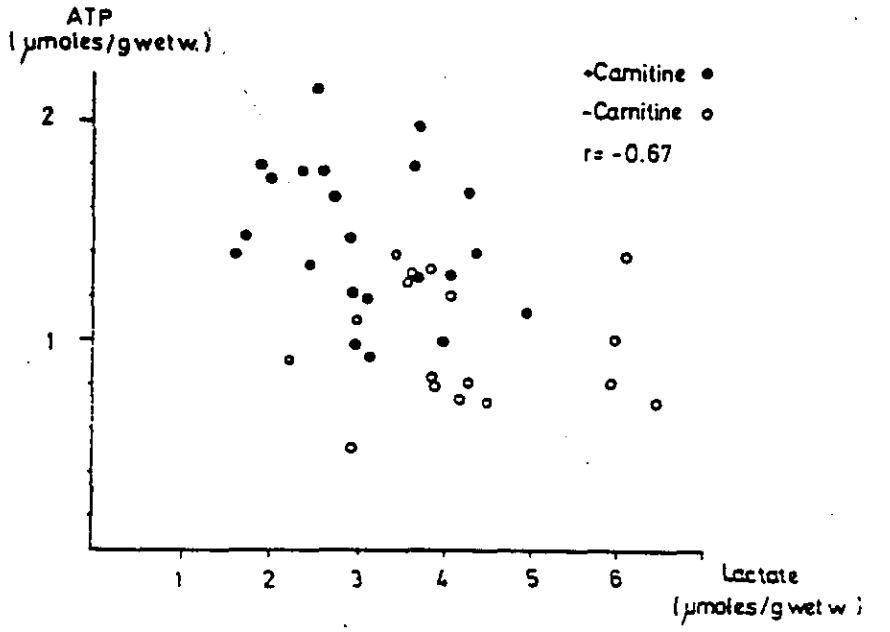

Figure 3. Relationship between ATP and lactate concentrations in the right atrial appendage of patients undergoing aorto-coronary bypass operation.

DISCUSSION

Recently, considerable attention has been focused on the role of carnitine in impaired fatty acid metabolism in ischemic myocardium.[1,5,9,10] It has been ascertained that anoxia or even ischemia cause an accumulation of long-chain fatty acids and their metabolites, in particular acyl-CoA and long-chain acylcarnitine,[11] with a concomitant decrease of free carnitine. This is either due to its leakage from the tissue or to its esterification.[12] Aorto-coronary bypass operation was performed on 68 patients after ischemic coronary heart disease had been proved by selective coronary angiography. The effect of oral carnitine supplementation on myocardial metabolites agrees with the results obtained in animal experiments,[13,14] in which the effect of carnitine on ischemic myocardium was tested. Pretreatment with L-carnitine prevented the decrease in free carnitine and the increase in long-chain acylcarnitine. The significance of this effect is expressed in higher ATP concentrations when carnitine is supplemented, because the function of essential enzymatic activities may be reestablished.[10] The lower myocardial lactate concentrations corresponding to higher ATP values may reflect the hemodynamic action of carnitine, resulting in better tissue oxygenation.[15] The lowering of lactate concentrations also

may be explained if one considers that ischemia causes an accumulation of long-chain acyl-CoA with an increase of the acyl-CoA/CoA ratio. This inhibits the activity of pyruvate dehydrogenase, the enzyme which regulates the entry of pyruvate into the citric acid cycle. Under these conditions, pyruvate is converted to lactate. L-carnitine may reduce lactate production either by activating pyruvate dehydrogenase directly or by provoking a decrease in the acyl-CoA/CoA ratio as a consequence of acyl removal from CoA.[16]

Our analysis of clinical and chemical data taken postoperatively from the charts of patients in ICU show that patients given carnitine had needed significantly less catecholamines than controls. This aspect fits into the described chemical cellular alterations. However, it should be interpreted with care because the use of catecholamines is a very subjective decision of the physician on duty. Input from medical house officers were not taken into consideration in our paired statistical analysis.

To see the effect of carnitine supplementation on serum carnitine concentrations, it would have been better to analyze preoperative blood samples. Our postoperative analysis, however, disclosed an interesting aspect. Only the serum concentrations of the supplemented patients remained within normal limits. Those of control patients decreased, in some even decreasing to values consistent with carnitine deficiency. This observation may have further implications for the intensive care of postoperative patients.

Preoperative L-carnitine supplementation in patients undergoing aorto-coronary bypass surgery was proved to be effective and beneficial with respect to the normalization of parameters of myocardial energy metabolism.

References

1. Shug AL, Thomsen JH, Folts JD, et al. Changes in tissue levels of carnitine and other metabolites during myocardial ischemia and anoxia. *Arch Biochem Biophys* 1978; 187:25.

2. Ho CH, Pande SV. On the specificity of the inhibition of adenine nucleotide translocase by long-chain acyl coenzyme A esters. *Biochim Biophys Acta* 1974; 369:86.

3. Bremer J, Norum KR. The mechanism of substrate inhibition of palmityl coenzyme A: Carnitine palmityltransferase by palmityl coenzyme A. *J Biol Chem* 1967; 242:1744.

4. Lamers JMJ, Hülsmann WC. Inhibition of (Na + K +)-stimulated ATPase of heart by fatty acids. *J Mol Cell Cardiol* 1977; 9:343.

5. Shrago E, Shug AL, Sul H, et al. Control of energy production in myocardial ischemia. *Circ Res* 1976; 38(Suppl 1):75.

6. Suzuki Y, Kamikawa T, Kobayashi A, et al. Effects of L-carnitine on tissue levels of

acylcarnitine acyl CoA and high energy phosphate in ischemic dog hearts. *Jpn Circ J* 1981; 45:687.

7. McGarry JD, Foster DW. An improved and simplified radioisotopic assay for the determination of free and esterified carnitine. *J Lipid Res* 1976; 17:277.
8. Lamprecht W, Trautschold I. Adenosine-5-triphosphate: Determination with hexokinase and glucose-6-phosphate dehydrogenase. *Methods Enzymat Anal* 1975; 4:2101.
9. Whitmer JT, Idell-Wenger JA, Rovetto MJ, Neely JR. Control of fatty acid metabolism in ischemic and hypoxic heart. *J Biol Chem* 1978; 253:4305.
10. Folts JD, Shug AL, Koke JR, Bittar N. Protection of ischemic myocardium with carnitine. *Am J Cardiol* 1978; 41:1209.
11. Liedtke AJ. Alterations of carbohydrate and lipid metabolism in the acute ischemic heart. *Prog Cardiovasc Dis* 1981; 23:321.
12. Shug AL, Paulson DJ. Fatty acid and carnitine linked abnormalities during ischemia and cardiomyopathy. In: *Advances in myocardiology*. New York: Plenum Press, 1985.
13. Suzuki Y, Kamikawa T, Kobayadshi A, Yamazaki N. Effects of L-carnitine on tissue levels of free fatty acid. Acyl CoA, and Acylcarnitine in ischemic heart. *Adv Myocardiol* 1983; 4:549.
14. Paulson DJ, Shug AL. Effects of carnitine on the ischemic arrested heart. *Basic Res Cardiol* 1982; 77:460.
15. Brooks H, Goldberg L, Holland R, et al. Carnitine-induced effects on cardia and peripheral hemodynamics. *J Clin Pharmacol* 1977; 17:561.
16. Ferrari R, Cucchini F, Visioli O. The metabolic effects of L-carnitine in angina pectoris. *Int J Cardiol* 1984; 5:213.