Clinical relevance of L-carnitine–supplemented total parenteral nutrition in postoperative trauma. Metabolic effects of continuous or acute carnitine administration with special reference to fat oxidation and nitrogen utilization.[1-3]

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ABSTRACT Carnitine-free total parenteral nutrition (TPN) is claimed to result in a carnitine deficiency with subsequent impairment of fat oxidation. The present study was designed to evaluate the possible benefit of carnitine supplementation on postoperative fat and nitrogen utilization. Sixteen patients undergoing total esophagectomy were evenly randomized and received TPN without or with L-carnitine supplementation (74 $\mu mol \cdot kg^{-1} \cdot d^{-1}$) during 11 postoperative days. On day 11, a 4-h infusion of L-carnitine (125 μmol/kg) was performed in both groups. The effect of supplementation was evaluated by indirect calorimetry, N balance, and repeated measurements of plasma lipids and ketone bodies. Irrespective of continuous or acute supplementation, respiratory quotient and fat oxidation were similarly maintained throughout the study in both groups whereas N balance appeared to be more favorable without carnitine. We conclude that carnitine-supplemented TPN does not improve fat oxidation or promote N utilization in the postoperative phase. *Am J Clin Nutr* 1989;49:283–9.

KEY WORDS L-carnitine, respiratory quotient, fat oxidation, total parenteral nutrition, nitrogen balance

Introduction

L-carnitine is required for the transport of long-chain free fatty acids into mitochondria for subsequent energy release by β-oxidation. In healthy subjects, the total body pool of carnitine is maintained by endogenous synthesis in liver and kidneys plus dietary intakes and is balanced by urinary excretion (1–3).

Surgical patients on total parenteral nutrition (TPN) do not usually receive carnitine and are known to excrete large amounts of this compound in urine during the postoperative course (4–5). Furthermore, surgical stress increases fat oxidation (6–7) and thus the need for carnitine might be enhanced. Another reasonable cause for carnitine deficiency might be insufficient synthesis due to possible liver and renal dysfunction.

Carnitine depletion, defined as low plasma levels, was reported in adult patients while on TPN for > 20 d (8–9). Only in a single study was carnitine deficiency monitored by a decreased rate of fat oxidation measured by indirect calorimetry (10), which showed a beneficial effect of carnitine supplementation on lipid utilization in septic patients receiving TPN without fat.

The present study was designed to examine, by indirect calorimetry and assessment of lipid metabolism and nitrogen retention, whether continuous or acute infusion of L-carnitine may beneficially influence postoperative fat oxidation and N balance in patients with esophageal carcinoma exhibiting cancer-induced malnutrition.

Materials and methods

Patients and controls

Sixteen patients undergoing total esophagectomy for epidermoid carcinoma were randomized into two groups to receive exclusive TPN either without (group A, $n = 8$) or with (group B; $n = 8$) L-carnitine supplementation during the postoperative period (**Table 1**). Operations included a thoracotomy and a laparotomy under general anesthesia (5.4 ± 1.4 h). All patients were postoperatively admitted to the intensive care unit for me-

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TABLE 1
Characteristics of patients of group A (TPN without L-carnitine) and of group B (TPN with L-carnitine) and of control subjects*

	Group A† (n = 8)	Group B‡ (n = 8)	Control subjects§ (n = 24)
Age (y)	62.7 ± 15.5	65.8 ± 8.6	27.0 ± 0.9‖
Weight (kg)			
Preoperative (day −1)	64.1 ± 2.8	64.2 ± 4.3	—
Postoperative (day 12)	63.4 ± 2.9	63.3 ± 4.3	—
Body surface (m^2)	1.72 ± 0.05	1.74 ± 0.06	1.65 ± 0.03

* $\bar{x}$ ± SEM.
† Three females, five males.
‡ Two females, six males.
§ Twelve females, 12 males.
‖ $p < 0.05$ groups A and B.

chanical ventilation for at least 2 d (3.3 ± 1.2 d). Exclusion criteria were liver cirrhosis with ascites, renal failure, hyperlipidemia, and endocrinological diseases. Each individual was orally informed about the nature of the investigations before participating in the study and gave informed consent. The procedures followed were in accord with the Helsinki Declaration as updated in Tokyo, Japan, 1975.

A control group of 24 healthy subjects was investigated as references for carnitine measurements in plasma and urine. For all other variables, the references were the values from our clinical laboratory.

Experimental design

TPN began on the first postoperative day and the nutrient intake was steadily increased until day 3 (**Table 2**). The full regimen provided 35 kcal·kg^{-1}·d^{-1} total energy (nonprotein energy from equal amounts of fat [Lipovenös® 20%, Fresenius AG, Bad Homburg, FRG] and glucose) and 1.0 g amino acids/kg per day (Proteinsteril® 10%, Fresenius AG). Electrolytes, trace elements, and vitamins were given as recommended (11). Nutrients were mixed in nutritional bags and infused continuously via a central venous catheter during the 13 consecutive postoperative days. Patients in group B were continuously supplemented with 74 μmol·kg^{-1}·d^{-1} L-carnitine until the 11th postoperative day. Parenteral nutrient intake was calculated daily by weighing the nutritional bags before and after infusion.

Indirect calorimetry measurements 1 h duration were performed on the preoperative day (day −1) after an overnight fast and on the 11th postoperative day (day 11a) without interrupting TPN. Immediately after the second calorimetric measurement, an intravenous 4-h infusion of 125 μmol L-carnitine/kg was provided to all patients irrespective of whether they received carnitine-containing TPN or not. Directly after the completion of the infusion, a third calorimetric measurement (day 11b) was performed and repeated 24 h later (day 12). Blood samples were obtained at the end of each measurement. Twenty-four-hour urine pools were collected the day before the operation and postoperatively with a vesical catheter on days 11–13. Urine collection on day 11 finished when the L-carnitine infusion began; collections thereafter were for day 12.

Indirect calorimetry

For indirect calorimetric measurements a calorimeter with a transparent ventilated hood built in Lausanne and described by Jéquier (12) was used. The energy expenditure (EE), respiratory quotient (RQ), lipid, carbohydrate, and protein oxidation rates were calculated from calorimetric values and urinary N excretion using the equations reported by Jéquier (12). The accuracy of the method has been shown to be within 1%. Heart rate (HR) and axillary temperature (T) were continuously monitored during the caloric measurements.

Carnitine

Blood samples in patients on day −1 and in control subjects were taken after an overnight fast. All subsequent blood samples in patients were taken early in the morning without modifying the TPN infusion rate. Free carnitine (FC), short-chain acylcarnitine (SCC), long-chain acylcarnitine (LCC), total acid-soluble carnitine (TASC), and the ratio of SCC and LCC to FC (AC:FC) were determined in plasma and urine as previously described by Rössle et al (13).

The carnitine balances on days 11 and 12 were calculated as the difference of the total carnitine intakes (amount administered with TPN in group B on day 11; amount of carnitine infused in both groups on day 12) and the total urinary carnitine outputs. After the 4-h infusion, TPN of both groups was carnitine free and the carnitine balances, therefore, were equal to total urinary carnitine outputs.

Laboratory

Plasma free fatty acids (FFA) were determined according to Heindel and Cushman (14), β-hydroxybutyrate (β-OH) and acetoacetate (AcAc) according to Mellanby and Williamson (15), and triglycerides (TG) according to Stavropoulos and Crouch (16). Total N in 24-h urine collections was measured by chemiluminescence (Auto-Analyzer 703 C, Antek Instruments, Inc, Houston Texas) (17). The apparent N balance was calculated as the N provided with TPN minus the total urinary N.

Statistics

All the results are expressed as mean ± standard error of the mean (SEM). Statistical differences were assessed using the nonparametric tests according to Mann-Whitney or Wilcoxon for unpaired or paired comparisons of the patients, respectively. For simultaneous comparisons of both patient groups with control subjects, analysis of variance (ANOVA) was used (18).

TABLE 2
Nutrients and L-carnitine intakes during the 13 postoperative days of patients in group A (TPN without L-carnitine) and in group B (TPN with L-carnitine)*

	Group A (n = 8)	Group B (n = 8)
Nutrients		
Energy (kcal·kg^{-1}·d^{-1})	34.7 ± 0.7	32.4 ± 1.3
Amino acids (g·kg^{-1}·d^{-1})	1.1 ± 0.1	1.0 ± 0.1
L-carnitine		
Continuous supplementation (μmol·kg^{-1}·d^{-1})	0	74.2 ± 2.6
4-h perfusion (μmol/kg)	123.1 ± 1.7	130.0 ± 2.8

* $\bar{x}$ ± SEM.

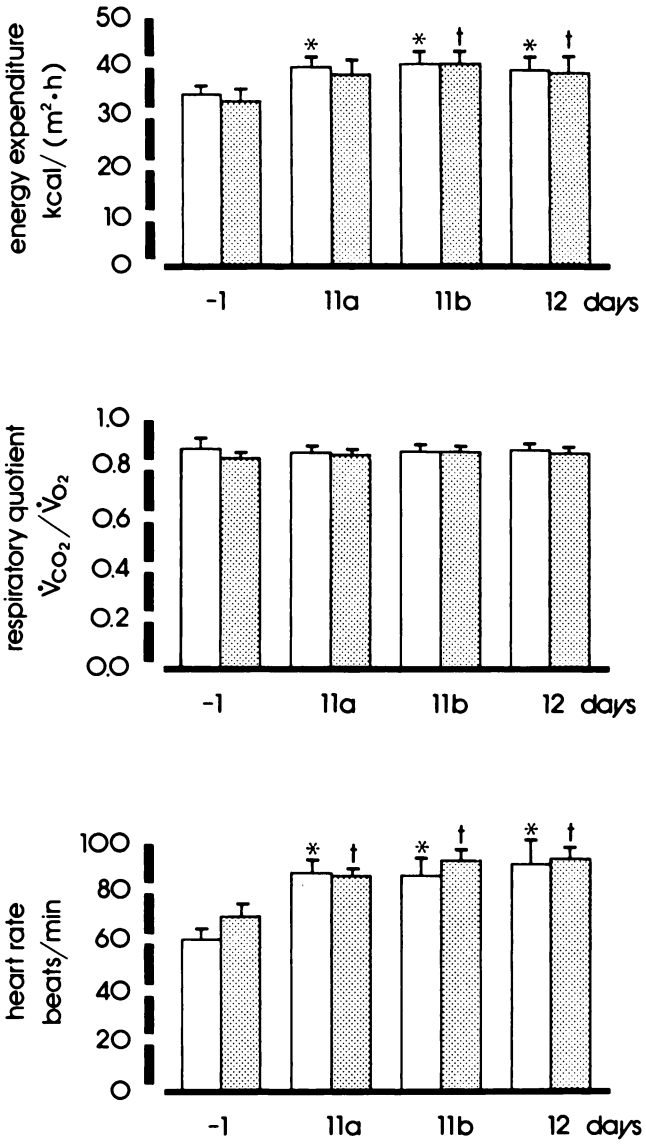

FIG 1. Energy expenditure, respiratory quotient, and heart rate on day −1, day 11a, day 11b, and day 12 in group A (□, TPN without L-carnitine) and in group B (□, TPN with L-carnitine) ($\bar{x} \pm$ SEM). *$p < 0.05$ vs day −1 group A and †$p < 0.05$ vs day −1 group B.

Results

Indirect calorimetry

Preoperative EE, RQ, and HR were fairly comparable in both groups (**Fig 1**). On day 11, EE and HR were increased to a similar extent ($r = 0.956$, $p < 0.01$) in groups A and B but RQ and T were unchanged. In response to the 4-h infusion of L-carnitine (day 11b), no modification of EE and RQ was observed. These results were confirmed 24 h later (day 12).

Preoperative substrate oxidation rates showed large individual variations in both groups (**Fig 2**). The subsequent measurements did not reveal systematic changes in relation to continuous or acute exogenous administration of L-carnitine. No differences in substrate oxidation rates were apparent between the study groups.

Plasma carnitine

Preoperative carnitine levels and AC:FC in groups A and B were similar although a comparison with normal values revealed slightly higher TC concentrations and significantly lower AC:FC (**Table 3**). After 11 d of postoperative treatment, patients in group A maintained the carnitine concentrations initially noted whereas those in group B exhibited elevated values as a consequence to the L-carnitine-supplemented TPN. In response to the 4-

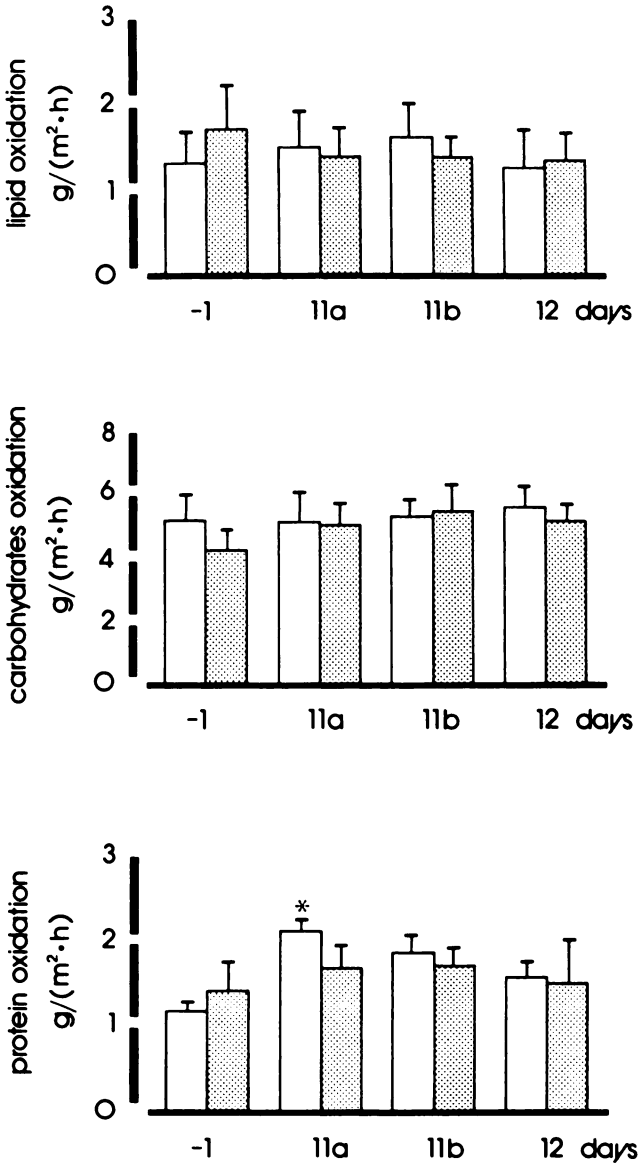

FIG 2. Lipid, carbohydrate, and protein oxidation rates on day −1, day 11a, day 11b, and day 12 in group A (□, TPN without L-carnitine) and in group B (□, TPN with L-carnitine) ($\bar{x} \pm$ SEM). *$p < 0.05$ vs day −1 group A.

TABLE 3
Plasma carnitine levels on day −1, day 11a, day 11b, and day 12 in group A (TPN without L-carnitine) and in group B (TPN with L-carnitine)*

	Free carnitine (FC)	Short-chain carnitine (SCC)	Long-chain carnitine (LCC)	Total carnitine (TC)	Carnitine ratio (AC:FC)†
			μmol/L		
Controls (n = 24)	36.9 ± 2.2	8.8 ± 0.7	3.6 ± 0.3	49.2 ± 2.8	0.35 ± 0.002
Group A (n = 8)					
Day − 1	44.9 ± 4.4	8.1 ± 1.2	2.7 ± 0.6	55.6 ± 4.8	0.23 ± 0.05‡
Day 11a	45.5 ± 6.3	5.7 ± 0.9	3.0 ± 1.0	54.2 ± 7.3	0.16 ± 0.02‡§
Day 11b	206.5 ± 16.5‡§‖	18.3 ± 4.1‡§‖	6.1 ± 1.1‡§‖	230.9 ± 12.4‡§‖	0.12 ± 0.02‡§
Day 12	54.7 ± 6.2	6.6 ± 0.9	3.2 ± 0.7	64.5 ± 7.1	0.18 ± 0.02‡
Group B (n = 8)					
Day − 1	47.7 ± 3.8	7.8 ± 1.5	2.8 ± 0.3	58.3 ± 4.3	0.23 ± 0.04‡
Day 11a	84.5 ± 6.8‡§¶	11.0 ± 2.9¶	3.3 ± 0.3	98.8 ± 9.3‡§¶	0.16 ± 0.03‡
Day 11b	220.0 ± 40.0‡§‖	15.2 ± 4.1‡§	6.7 ± 1.3‡§‖	241.9 ± 52.8‡§‖	0.10 ± 0.02‡§‖
Day 12	88.9 ± 7.7‡§¶	10.7 ± 1.8¶	3.6 ± 0.4	103.2 ± 9.6‡§¶	0.16 ± 0.01‡

* $\bar{x}$ ± SEM.
† The ratio of SCC and LCC to FC.
‡ $p < 0.05$ vs control subjects.
§ $p < 0.05$ vs day −1 same group.
‖ $p < 0.05$ vs day 11a same group.
¶ $p < 0.05$ vs same day group A.

h infusion of L-carnitine on day 11, the concentration of TC as well as the levels of its subfractions were markedly increased in both groups whereas AC:FC was decreased. One day after the infusion, carnitine levels and AC:FC in both groups returned to the levels observed before the infusion.

Urinary carnitine

Preoperative urinary output of TASC and AC:FC were similar in both groups (**Table 4**). In comparison with the control subjects, the excretion of FC and TASC were somewhat elevated and AC:FC was markedly decreased. LCC excretions were not measured because they were shown to be negligible, representing at most 2% of TC (C Rössle unpublished observations, 1987). On day 11 carnitine excretions were still higher than preoperative values in group A and were largely increased in group B. As the extent of increase in acylcarnitines was less pronounced than that of FC, AC:FC was markedly decreased in both groups. One day after infusion (day

TABLE 4
Urinary carnitine excretions on day −1, day 11a, day 12, and day 13 group A (TPN without L-carnitine) and in group B (TPN with L-carnitine)*

	Free carnitine (FC)	Short-chain carnitine (SCC)	Total carnitine (TASC)	Carnitine ratio (AC:FC)†
		μmol/L		
Control subjects (n = 24)	180 ± 23	225 ± 27	405 ± 48	1.77 ± 0.18
Group A (n = 8)				
Day − 1	299 ± 93	195 ± 37	494 ± 100	1.19 ± 0.56‡
Day 11a	426 ± 95‡	286 ± 56	712 ± 137‡	0.77 ± 0.17‡§
Day 12	4980 ± 471‡§	916 ± 189‡§	5895 ± 571‡§	0.30 ± 0.10‡§
Day 13	1040 ± 322‡§	444 ± 169§	1484 ± 497‡§	0.42 ± 0.07‡§
Group B (n = 8)				
Day − 1	232 ± 71	209 ± 60	441 ± 106	1.04 ± 0.18‡
Day 11a	4900 ± 727‡§‖	980 ± 115‡§‖	5880 ± 826‡§‖	0.21 ± 0.02‡§‖
Day 12	9826 ± 1067‡§‖	1796 ± 461‡§‖	11622 ± 699‡§‖	0.42 ± 0.19‡§
Day 13	3719 ± 789‡§‖	819 ± 142‡§‖	4538 ± 893‡§‖	0.23 ± 0.04‡§‖

* $\bar{x}$ ± SEM.
† The ratio of SCC and LCC to FC.
‡ $p < 0.05$ vs control subjects.
§ $p < 0.05$ vs day −1 same group.
‖ $p < 0.05$ vs same day group A.

12), the urinary TASC outputs were further increased in both groups but returned to levels comparable to that noted before the infusion the next day.

Carnitine balance

The carnitine balances of the 11th postoperative day were similarly negative in groups A and B (−712 ± 137 and −784 ± 745 μmol/d, respectively). The balances on day 12 became positive in both groups A (1787 ± 421 μmol/d) and B (2349 ± 721 μmol/d) as a response to the carnitine infusion. Importantly, in group A a negative balance was observed on the next day (−1484 ± 497 μmol/d), whereas in group B the mean balance was still positive (188 ± 1757 μmol/d) although there were considerable individual variations.

Plasma lipids

Preoperative values compared fairly in both groups and with control subjects (**Table 5**). On day 11 the variables of lipid metabolism measured were not changed compared with preoperative concentrations, nor were alterations observed after the 4-h infusion of L-carnitine. A slight elevation of ketone body levels might be apparent in group B patients until the 11th postoperative day. However, acute infusion of relatively high amounts of carnitine resulted in a drop in the concentration of ketone bodies in both groups (day 11b). The calculated ratios of FFA and TG and FFA and β-OH levels (data not given) were similar in both groups.

Apparent nitrogen balance

Preoperative urinary N losses were similar in both groups A and B (630 ± 60 and 790 ± 60 mmol/d, respectively). On day 11 the apparent N balance was actually more favorable in group A (−120 ± 60 mmol/d) than in group B (−290 ± 180 mmol/d). Interestingly, the 4-h infusion of L-carnitine further underlined the above observation; the balances estimated on day 12 being 10 ± 60 and −350 ± 110 mmol/d, respectively. However, on the next day the apparent N balances did not differ, exhibiting −270 ± 120 and −260 ± 150 mmol/d, respectively.

Discussion

This study examines the clinical relevance of carnitine supplementation in surgical patients requiring parenteral nutrition postoperatively. In daily practice, the majority of these patients requires such nutritional support for < 2 wk (19). To collect homogenous population we selected patients undergoing the same major elective operation, ie, esophagectomy. In 10 of the patients, surgical muscle biopsies could be performed before the operation and the results revealed a considerably diminished total-body-carnitine pool compared with that found in healthy control subjects (75 vs 131 mmol) (20, 21). The total-body-carnitine pool was estimated from the measured total carnitine concentration in muscle specimens and by considering the muscle mass, assuming that the total-body-carnitine pool is virtually identical with the muscle pool (22) and that 8.85 mmol/d creatinine excretion is equivalent to 20 kg of muscle tissue (23). This finding is assumed to be the result of a reduced oral carnitine intake in these patients because of cancer-induced chronic semistarvation (24, 25). Therefore, the presently investigated patients are undoubtedly already carnitine-deficient before the operation although this was not evident from plasma and urinary carnitine levels. It is to be expected that this carnitine deficiency will be accentuated in the postoperative phase as a consequence of the known trauma-induced excessive urinary carnitine losses (4, 5). Thus, the investigated patients are supposed to represent an adequate population for evaluation of possible beneficial effects of carnitine-supplemented TPN on postoperative fat and N utilization. Their preoperative measured EE was consistent with the predictive formulas described by Fleisch in normal subjects (26). The approximately 10% increased EE reported in cancer patients is still debatable (27) and was not observed in the present study. The increase might be explained by the patients' preoperative weight loss (8.3 ± 2.7 kg during the last 3 mo); protein and energy malnutrition are known to reduce EE (7).

The mild increased postoperative EE measured at day 11 was probably related to the effect of residual surgical stress and diet-induced thermogenesis. This enhanced EE was consistent with higher HR. The acute infusion of carnitine did not lead to hyperthermia and higher oxygen consumption as reported on two septic and hemodialyzed patients on TPN (28).

Overnight fasting preoperative RQ was relatively elevated compared with normal control subjects (29). This might be due to some degree of hyperventilation (30) related to preoperative fear. Because postoperative RQ was similar whether or not the patients received continuous carnitine supplementation, it is conceivable to suggest that when there is a relative carnitine deficiency, normal fat oxidation might subsist because sufficient amounts of carnitine in the pool are still available. This finding is highly supported by the fact that the acute infusion did not change the RQ despite a high transient carnitine retardation in both groups. Similar findings were recently reported by Nanni et al (10) in nonseptic patients on hypocaloric fat-free parenteral nutrition with D,Lacetylcarnitine supplementation for 20 d, whereas a decrease in the RQ was observed in septic patients revealing extremely high EE. Because none of the three septic patients in the present study survived until the completion of the study, we are not able to discuss the observation made by Nanni et al (10).

Postoperative RQ was close to the calculated RQ of the infused nutrients (ie, 0.85), thus the proportion of oxidized fat, carbohydrate, and amino acids matched those administered by TPN. Although the duration of the calorimetric measurements was relatively short (1 h), the within-individual variability in both EE and RQ during the whole day is small when the nutrients are admin-

TABLE 5
Plasma triglycerides, free fatty acids, and ketone bodies on day −1, day 11a, day 11b, and day 12 in group A (TPN without L-carnitine) and in group B (TPN with L-carnitine)

	Triglycerides (TG)	Free fatty acids (FFA)	β-hydroxybutyrate (β-OH)	Acetoacetate (AcAc)
			μmol/L	
Control subjects (n = 24)	[870–1560]	[300–700]	[58–170]	[18–78]
Group A (n = 8)*				
Day − 1	1297 ± 171	430 ± 103	147 ± 12	31 ± 13
Day 11a	1210 ± 245	543 ± 63	178 ± 34	45 ± 12
Day 11b	1264 ± 289	500 ± 82	115 ± 18†	22 ± 4†
Day 12	1220 ± 252	580 ± 52	137 ± 8†	26 ± 3†
Group B (n = 8)*				
Day − 1	1825 ± 304	461 ± 65	217 ± 43	47 ± 13
Day 11a	1354 ± 183	482 ± 75	272 ± 64	40 ± 7
Day 11b	1341 ± 144	499 ± 90	211 ± 34‡	29 ± 7
Day 12	1456 ± 245	439 ± 69‡	331 ± 106‡	30 ± 6

* $\bar{x}$ ± SEM.
† $p < 0.05$ vs day 11a same group.
‡ $p < 0.05$ vs same day group A.

istered at a constant flow (31). The range of possible RQ values was narrowed by the continuous nutrient infusion, therefore, a potential decrease in RQ related to carnitine would be so small that the large interindividual variations observed in substrates oxidation rates might occult them.

Because the majority of continuously- or acutely-infused carnitine was excreted in the free form, only very small endogenous acylation seems to take place. This finding suggests that the administered carnitine is apparently little used for transport of acyl groups. Recently, Böhles et al (32) reported a ketogenic or antiketogenic response to a low and high carnitine supply, respectively, in experimental rats. In the present study slightly increased levels of ketone bodies were observed during continuous carnitine supply when infused at a low rate, whereas acute carnitine administration with excessive amounts resulted in a decreased concentration of β-OH and AcAc in plasma, thus supporting the dose-dependent effect of carnitine in ketogenesis as postulated by Böhles et al (32).

The small variations in triglyceride concentrations reflect most probably the constant rate of triglycerides infusion and indicate their continuous elimination of plasma. Our data do not conform with results that claim a carnitine-mediated improvement of the N balance (N sparing effect) by increasing the portion of energy derived from fat in total EE. In contrast, we observed an inferior N balance in patients receiving carnitine-supplemented TPN presumably because of a competitive inhibition of amino-acid absorption by carnitine in the proximal renal tubules resulting in augmented urinary amino acid (N) losses. This supposed effect is especially apparent after the acute infusion of carnitine. The increased N losses indeed represent a side effect of excessive carnitine supplementation and should be seriously contemplated.

In conclusion, continuous carnitine supplementation of surgical patients receiving postoperative TPN for 2 wk failed to beneficially influence fat oxidation and N balance. It is conceivable that carnitine-free TPN for 11 d does not accentuate carnitine deficiency because acute infusion did not affect fat oxidation.

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