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Plasma Carnitine Levels and Urinary Carnitine Excretion during Sepsis

GIUSEPPE NANNI, M.D., MAURO PITTIRUTI, M.D., IVO GIOVANNINI, M.D., GIUSEPPE BOLDRINI, M.D., PAOLO RONCONI, M.D., AND MARCO CASTAGNETO, M.D.

From the Centro di Studio per la Fisiopatologia dello Shock, CNR and Istituto di Clinica Chirurgica Generale e Terapia Chirurgica, Universita' Cattolica del Sacro Cuore, Roma, Italy

ABSTRACT. Carnitine is an indispensable factor for the β-oxidation of medium- and long-chain fatty acids, and it plays a possible role in the oxidation of branched-chain amino acids. Plasma and urinary levels of free carnitine and short-chain acyl-carnitines were studied in 67 surgical patients, after nonseptic surgical procedures or during sepsis. The septic state was associated with increased urinary excretion of free carnitine ($p < 0.001$), as well as with lower plasma levels of short-chain acyl-carnitines ($p < 0.001$); the latter feature correlated with the level of hypermetabolism, as evaluated by the metabolic rate and by the arterial-mixed venous O_2 difference. In 26 patients during total parenteral nutrition D, L-acetyl-carnitine was administered (100 mg/kg/24 hrs, in continous iv infusion) and was associated, in septic patients only, with a significant decrease in the respiratory quotient, suggesting enhanced oxidation of low respiratory quotient substrates (fatty acids and/or branched-chain amino acids). Carnitine supplementation during total parenteral nutrition might be of theoretical benefit in some clinical conditions, such as sepsis, in which the following conditions coexist (1) enhanced utilization of substrates whose oxidation is partially or totally carnitine dependent; (2) prolonged absence of exogenous intake of carnitine (as in long-term total parenteral nutrition); (3) eventual impairment of carnitine synthesis due to hepatic dysfunction; (4) increased, massive urinary loss of carnitine. (*Journal of Parenteral and Enteral Nutrition* **9**:483–490, 1985)

The physiologic response to sepsis is qualitatively different from the response to nonseptic injury, since it is characterized by a derangement of intermediary metabolism, resulting in complex interactions between cardiac, vascular, and pulmonary mechanisms.[1–3] In recent years, a great number of studies have identified the main abnormalities of this acquired metabolic disorder: glucose intolerance with "insulin resistance";[4] hypermetabolism with increased protein catabolism and muscle wasting;[5] exaggerated gluconeogenesis;[6] preferential oxidation of endogenous substrates such as fatty acids and branched-chain amino acids;[7–9] progressive metabolic insufficiency leading to multiple organ failure.[10,11] The difficulty in the management of the septic patient lies in the fact that nutritional therapy is able to correct problems of substrate delivery (such as in malnourished medical patients) but cannot deal satisfactorily with disorders of substrate processing (such as in critically ill patients).[8,12] Only a better understanding of the metabolic mechanisms altered in the septic state may lead in the future to a selective correction of specific defects in the utilization of substrates.

The analysis of the changes in carnitine metabolism in the critically ill may yield an important contribution for the assessment of the degree of metabolic derangement, since carnitine plays a key role in many oxidative pathways.

Carnitine is indispensable for the β-oxidation of medium- and long-chain fatty acids, because of its role as carrier of fatty acid acyl residues across the internal membrane of mitochondria;[13] it modulates the acyl-CoA/CoASH ratio, thus regulating the activity of pyruvate dehydrogenase and of Krebs cycle;[14] it increases branched-chain amino acids oxidation in muscular tissues;[15–17] it may have several other obligatory or facultative roles (eg, regulation of ketogenesis; shuttle of chain-shortened products out of peroxisomes; translocation of acetyl units for selective acyl residues; etc.).[14]

In the present study, we have investigated plasma and urinary levels of free carnitine (FC) and short-chain acyl carnitines (AC) in surgical patients, after nonseptic surgical procedure or during sepsis.

MATERIALS AND METHODS

Patients

Study without AC administration. One hundred forty-four physiologic-metabolic studies were performed in 67 patients: 73 studies in 40 patients after nonseptic surgical procedure and 71 studies in 27 septic patients. In both groups, patients with hepatic or renal failure (serum creatinine higher than 2 mg/100 ml) were excluded.

The first group of patients (nonseptic surgery) consisted of 73 studies in 40 patients: 35 patients in the postoperative period after major surgery for biliary, pancreatic, gastrointestinal, or thoracic diseases (28 neoplastic patients) and five patients after acute pancreatitis. The studies were performed in the period between the 1st and the 20th day after surgery or onset of acute pancreatitits; half of the studies were performed before the 5th day. Eleven studies were performed in females (four patients), 62 in males (36 patients). The number of studies for each patient ranged from one to five. In this group, mean age was 61 ± 10 yr; mean weight was 74 ± 11 kg; mean body surface area (BSA) was 1.72 ± 0.16 m^2,

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Reprint requests to: Mauro Pittiruti, M.D., Via Pereira 246, 00136 Roma, Italy.

and mean basal energy expenditure (BEE) (according to the Harris-Benedict formula) was 790 ± 109 kcal/m^2/24 hr. All studies were performed during total parenteral nutrition (TPN), with no oral intake; nutrition consisted of infusion of glucose calories (570 ± 477 kcal/m^2/24 hr), solutions of amino acids (4.6 ± 2 g N/m^2/24 hr), without lipid infusion. Insulin was added when required (only in seven patients).

The second group (sepsis) consisted of 71 studies in 27 patients with overt sepsis (mainly diffuse peritonitis or intrabdominal abscess, plus one patient with pulmonary sepsis); the diagnosis of sepsis had been established by the presence of hyperpyrexia, positive blood culture, or positive culture from abdominal drainage, plus a cardiorespiratory pattern typical of the septic state.[18,19] The studies were performed starting from the 2nd day after the diagnosis of sepsis had been established, up to the 16th day of the septic clinical course. Most patients in this group had undergone surgical procedure, either as treatment of abdominal disease, before the onset of sepsis, or as drainage of the source of sepsis. Twelve patients in this group had neoplastic disease. The number of studies in each patient ranged from one to nine. Only one patient was female (two studies). Mean age of the patients was 52 ± 18 yr; mean weight was 65 ± 11 kg; mean BSA was 1.74 ± 0.2 m^2; mean BEE was 830 ± 111 kcal/m^2/24 hr. All of these patients were studied on TPN, with no oral intake: infusion of glucose (816 ± 534 kcal/m^2/24 hr) and amino acids solutions (6 ± 2.6 g N/m^2/24 hr), no lipid infusion. Only seven patients required insulin administration.

All patients, both in the nonseptic group and in the septic group, received a daily amount of lysine (precursor of carnitine synthesis), in parenteral fluids, ranging from 2.3 to 3.15 g/m^2/24 hr.

Study with AC administration. We also performed 48 studies during TPN (no lipid infusion, no oral intake) adding D, L-AC (100 mg/kg/24 hr, in continous iv infusion); in an average 70-kg patient, this daily dosage corresponds to almost 32 mmol of acetate (2 kcal) and 32 mmol of D, L-carnitine.

Twenty-two studies were performed in 14 nonseptic postoperative patients (14 studies in 11 males and eight studies in three females; mean age = 58 ± 14 yr; mean weight = 57 ± 9 kg; BSA = 1.61 ± 0.13 m^2; BEE = 790 ± 120 kcal/m^2/24 hr; glucose calories = 720 ± 596 kcal/m^2/24 hr; nitrogen = 5.3 ± 3.7 g N/m^2/24 hr; insulin was required in three patients), while 26 studies were performed in 12 male septic patients (mean age = 41 ± 17 yr; mean weight = 72 ± 9 kg; BSA = 1.83 ± 0.15 m^2; BEE = 893 ± 107 kcal/m^2/24 hr; glucose calories = 716 ± 656 kcal/m^2/24 hr; nitrogen = 6.3 ± 3.3 g N/m^2/24 hr; insulin was required in four patients).

Patients with hepatic disease or renal failure were not included in this study. Eight of 14 nonseptic surgical patients and all but one septic patients had been previously studied without carnitine administration and included in the protocol described above.

Controls. Twenty metabolic studies were also performed in 20 patients in the preoperative period, before elective surgery for abdominal disease, without renal failure, without hepatic disease, or major cardiovascular abnormalities. None of them had evidence of infection or malnutrition. They were all on standard oral diet. The group included three females; mean age was 62 ± 12 yr; mean weight was 66 ± 13 kg; BSA was 1.73 ± 0.2 m^2.

Methods

Each study consisted of simultaneous measurement of metabolic and cardiorespiratory data.

Metabolic data. Metabolic studies were performed on heparinized arterial blood. On the day of the study, urine was collected and a 24-hr sample was taken for determination of FC and esterified carnitine (the amount of carnitine excreted was referred to the total daily urine output and expressed in μmol/24 hr). Carnitine excretion from gastrointestinal tract was not measured.

Several metabolites were measured in plasma—free fatty acids, triglycerides, cholesterol, and phospholipids were determined by previously described methods;[20–23] lactate, pyruvate, acetoacetate, and β-hydroxybutyrate were determined by enzymatic fluorimetric micromethod;[24] plasma values of glucose, carnitine, albumin, etc. were also obtained, by automated procedure (SMA autoanalyzer).

Carnitine concentration in serum and urine was determined by enzymatic method.[25] Each sample was analyzed with respect to both FC and short-chain AC (chains up to 10 C). The normal range, according to our laboratory, was 40–50 μmol/liter for serum FC and 10 to 15 μmol/liter for serum short-chain AC.

Cardiorespiratory data. Cardiorespiratory measurement were based, according to a previously developed method,[3,26,27] on simultaneous collection of samples of expired air (by Douglas bag) and arterial and central mixed venous blood. Oxygen and carbon dioxide partial pressures in expired air and in blood samples were determined using a IL 213 pH-gas analyzer. These data, together with expired minute volume measured on a Wright spirometer and other necessary data, were converted into a set of metabolic and hemodynamic parameters by use of a desk calculator.

Oxygen consumption (ml/min/m^2) and carbon dioxide production (ml/min/m^2) were calculated according to conventional formulas; respiratory quotient (RQ) was obtained as CO_2 production/O_2 consumption ratio; metabolic rate (MR) (kcal/m^2/24 hr) was obtained by a previously published computational method.[28] Theoretical BEE was assessed in each patient according to the Harris-Benedict formula.[29]

Statistical analysis. Wilcoxon's test, Student's *t*-test[30] and regression and covariance analysis[31] were used to establish statistical significance. Variance of the mean was expressed as SD of the mean.

RESULTS

Table I reports the mean values of plasma and urinary metabolites in 20 preoperative patients used as controls (20 studies). All values were in the normal range, according to our laboratory's standards.

Table IIa shows the mean values of plasma and urinary levels of FC and short chain AC in nonseptic surgical

patients and in septic patients, as well as the AC/FC ratio in plasma. No difference was observed in plasma FC between septics and nonseptics (46 ± 26 *vs* 44 ± 17 μmol/liter, respectively), while AC values were significantly lower in sepsis in comparison with nonseptic surgery (6.2 ± 3.4 *vs* 13 ± 13 μmol/liter; $p < 0.001$); a significant difference was also observed between AC/FC in sepsis and in nonseptic surgery (0.17 ± 0.13 *vs* 0.28 ± 0.2; $p < 0.001$). Regarding daily urinary excretion, FC excretion was significantly higher in septics than in nonseptics (951 ± 840 *vs* 392 ± 274 μmol/24 hr; $p < 0.001$), while no difference was observed in AC excretion. In comparison with control values (reported in Table I) significant differences were found only in septic patients, who had lower plasma AC ($p < 0.005$) and lower AC/FC ($p < 0.025$) (*t*-test), and higher urinary excretion of FC ($p < 0.05$) (Wilcoxon).

Table IIIa shows the mean values of O_2 consumption, CO_2 production, RQ, MR, and arterial-mixed venous O_2 content difference. Septic patients had higher MR than nonseptic patients ($p < 0.02$), with a higher MR/BEE ratio ($p < 0.05$); both O_2 consumption and CO_2 produc-

TABLE I
Control levels of plasma and urinary metabolites[a]

Plasma levels	
FC (μmol/liter)	36 ± 9
AC (μmol/liter)	10 ± 6.4
AC/FC	0.26 ± 0.21
GLU (mg/100 ml)	118 ± 34
PYR (μmol/liter)	99 ± 43
LAC (μmol/liter)	682 ± 220
PYR/LAC	0.17 ± 0.11
LIP (mg/100 ml)	777 ± 183
TG (mg/100 ml)	118 ± 48
PL (mg/100 ml)	135 ± 86
CHO (mg/100 ml)	144 ± 36
FFA (μEq/liter)	598 ± 382
AcAc (μmol/liter)	60 ± 85
BOH (μmol/liter)	241 ± 177
Urinary levels	
FC (μmol/24 hr)	269 ± 215
AC (μmol/24 hr)	143 ± 176

[a] Mean ± SD of FC and short-chain AC levels in plasma and urine, plus plasma levels of several metabolites in 20 preoperative patients used as controls (20 studies). GLU, glucose; PYR, pyruvate; LAC, lactate; LIP, total plasma lipids; TG, triglycerides; PL, phospholipids; CHO, total cholesterol; AcAc, acetoacetate; BOH, β-hydroxy-butyrate.

TABLE III
Physiologic parameters after nonseptic surgery and during sepsis[a]

	Surgery n	Surgery Mean ± SD	Sepsis n	Sepsis Mean ± SD	
a. Without AC infusion					*t*-test[b]
MR	26	984 ± 240	26	1200 ± 384	$p < 0.02$
Gluc/MR	29	0.83 ± 0.7	28	0.69 ± 0.6	NS
MR/BEE	34	1.19 ± 0.33	29	1.38 ± 0.4	$p < 0.05$
$\dot{V}CO_2$	26	140 ± 39	26	170 ± 42	$p < 0.001$
$\dot{V}O_2$	26	134 ± 35	26	169 ± 61	$p < 0.05$
RQ	26	1.07 ± 0.27	26	1.03 ± 0.18	NS
a-$\dot{v}DO_2$	36	4 ± 1.4	32	3.55 ± 1.15	NS

	Surgery n	Surgery Mean ± SD	*t*-test[c]	Sepsis n	Sepsis Mean ± SD	*t*-test[c]
b. During AC infusion						
MR	12	1128 ± 552	NS	12	1248 ± 408	NS
$\dot{V}CO_2$	12	145 ± 80	NS	12	143 ± 30	$p < 0.05$
$\dot{V}O_2$	12	132 ± 20	NS	12	179 ± 62	NS
RQ	12	1.00 ± 0.38	NS	12	.87 ± .19	$p < 0.02$

[a] Mean ± SD of physiologic parameters after nonseptic surgical procedure and during sepsis, in basal state (IIIa) or during continuous iv infusion of D,L-AC (100 mg/kg/24 hr) (IIIb). MR, kcal/m²/24 hr; ratio between glucose calories (kcal/m²/24 hr) and MR; ratio between MR and BEE; CO_2 production ($\dot{V}CO_2$), ml/min/m²; oxygen consumption ($\dot{V}O_2$), ml/min/m²; arterial-mixed venous O_2 content difference (a-$\dot{v}DO_2$), ml/100 ml.
[b] Statistical significance of differences between surgery and sepsis.
[c] Statistical significance of differences in parts a *vs* b.

TABLE II
Plasma and urinary levels of free and esterified carnitines, after nonseptic surgery and during sepsis[a]

	Surgery n	Surgery Mean ± SD	Sepsis n	Sepsis Mean ± SD	
a. Without AC infusion					*t*-test[b]
Plasma FC	67	44 ± 17	53	46 ± 26	NS
Plasma AC	57	13 ± 13	48	6.2 ± 3.4	$p < 0.001$
Plasma AC/FC	57	0.28 ± 0.2	48	0.17 ± 0.13	$p < 0.001$
					Wilcoxon[b]
Urine FC	41	392 ± 274	42	951 ± 840	$p < 0.001$
Urine AC	30	296 ± 473	27	263 ± 201	NS

	Surgery n	Surgery Mean ± SD	*t*-test	Sepsis n	Sepsis Mean ± SD	*t*-test[c]
b. During AC infusion						
Plasma FC	20	79 ± 36	$p < 0.001$	24	59 ± 26	$p < 0.05$
Plasma AC	17	78 ± 40	$p < 0.001$	21	25 ± 21	$p < 0.001$
Plasma AC/FC	17	0.92 ± 0.5	$p < 0.001$	20	0.36 ± 0.22	$p < 0.001$
			Wilcoxon**			Wilcoxon[c]
Urine FC	7	3786 ± 3132	$p < 0.001$	13	3678 ± 2264	$p < 0.001$
Urine AC	4	2844 ± 1758	$p < 0.001$	7	2323 ± 988	$p < 0.001$

[a] Mean ± SD of plasma and urinary levels of FC and short-chain AC, after nonseptic surgical procedure and during sepsis, in basal state (IIa) or during continuous iv infusion of D,L-AC (100 mg/kg/24 hr) (IIb).
[b] Statistical significance of differences between surgery and sepsis.
[c] Statistical significance of differences in parts a *vs* b (before *vs* after AC infusion, in each group).

tion were higher in septic patients ($p < 0.05$ and $p < 0.001$, respectively) if compared to nonseptics.

Table IVa reports the mean values of glucose and lipid parameters in nonseptic patients and in septics; plasma pyruvate, plasma pyruvate/lactate ratio, and plasma total cholesterol were significantly lower in septics. Total lipids were lower in sepsis than in nonseptic surgery ($p < 0.005$), but they were within the normal range in both groups.

We looked for statistical relationships between these abnormalities of plasma AC in sepsis and other physiologic parameters which are considered indicators of the hypermetabolic and hyperdynamic state of sepsis. A significant correlation was found between plasma AC and MR, but only in septic patients ($n = 24$; $r^2 = 0.37$; $F = 12.9$; $p < 0.01$) (see Fig. 1). A significant multiple correlation was also found, only in septic patients, between arterial-venous O_2 difference, plasma free fatty acids,

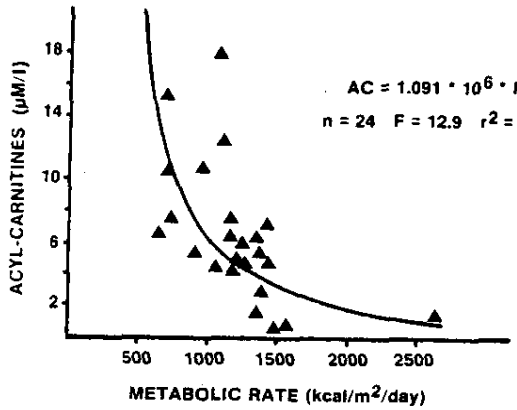

FIG. 1. Correlation between MR and plasma levels of short chain AC in septic patients, without AC infusion.

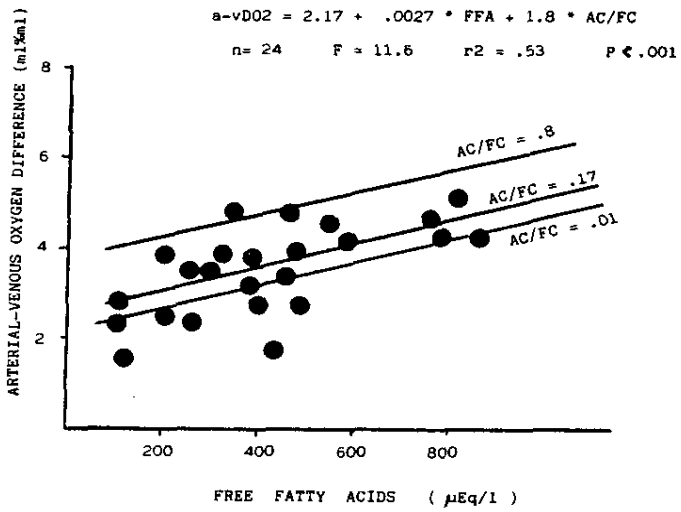

FIG. 2. Multiple correlation between arterial-venous O_2 content difference (a-$\bar{v}DO_2$), plasma levels of FFA, and plasma AC/FC ratio, in septic patients without AC infusion.

TABLE IV
Plasma metabolites after nonseptic surgery and during sepsis[a]

	Surgery			Sepsis		
	n	Mean ± SD		n	Mean ± SD	
a. Without AC infusion						*t*-test[b]
GLU	59	139 ± 65		57	146 ± 58	NS
PYR	50	108 ± 80		39	68 ± 36	$p < 0.01$
LAC	50	1460 ± 707		37	1526 ± 510	NS
PYR/LAC	50	0.11 ± 0.13		37	0.055 ± 0.05	$p < 0.03$
LIP	27	687 ± 181		34	548 ± 134	$p < 0.005$
TG	69	134 ± 61		53	126 ± 59	NS
PL	69	145 ± 62		53	128 ± 47	NS
CHO	68	133 ± 44		53	86 ± 19	$p < 0.0001$
FFA	68	456 ± 286		50	372 ± 251	NS
AcAc	40	66 ± 99		35	54 ± 55	NS
BOH	56	140 ± 157		35	113 ± 78	NS

	Surgery			Sepsis		
	n	Mean ± SD		n	Mean ± SD	
b. During AC infusion			*t*-test[c]			*t*-test[c]
GLU	19	120 ± 20	NS	20	123 ± 52	NS
PYR	18	106 ± 78	NS	15	92 ± 90	NS
LAC	18	1580 ± 565	NS	15	1381 ± 498	NS
PYR/LAC	18	0.09 ± 0.09	NS	14	0.07 ± 0.06	NS
LIP	19	684 ± 155	NS	18	540 ± 164	NS
TG	21	103 ± 60	$p < 0.05$	24	122 ± 48	NS
PL	21	140 ± 55	NS	24	114 ± 39	NS
CHO	21	124 ± 29	NS	24	87 ± 23	NS
FFA	21	431 ± 295	NS	21	406 ± 177	NS
AcAc	17	61 ± 42	NS	17	62 ± 45	NS
BOH	18	88 ± 68	NS ($p < 0.15$)	18	87 ± 48	NS ($p < 0.10$)

[a] Mean ± SD of parameters of glucose and lipid metabolism, after nonseptic surgical procedure and during sepsis, on TPN (IVa) and on TPN plus continuous iv infusion of D,L-AC (100 mg/kg/24 hr) (IVb). (For abbreviations and units see legend of Table I.)
[b] Statistical significance of differences between surgery and sepsis.
[c] Statistical significance of differences in parts a *vs* b.

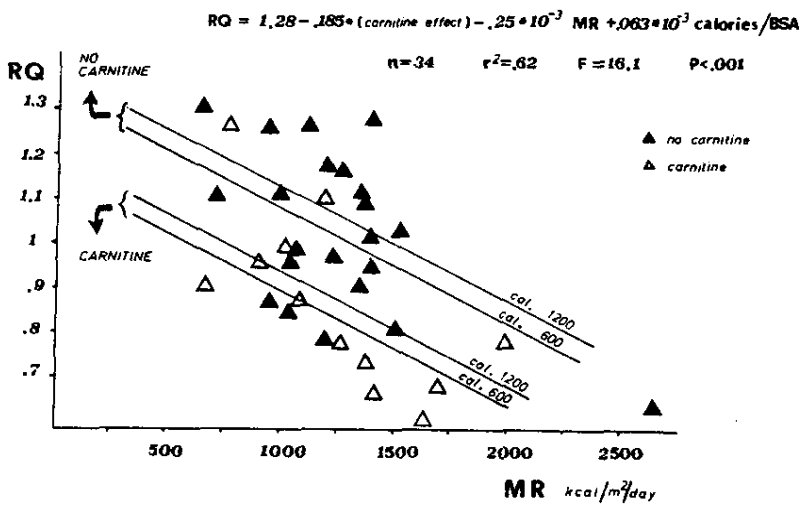

FIG. 3. Multiple correlation between RQ, MR, and mean value of daily intake of glucose calories (cal/BSA), in septic patients in relation to the effect of AC infusion.

and AC/FC ratio ($n = 24$; $r^2 = 0.53$; F = 11.6; $p < 0.001$) (see Fig. 2).

Study with AC administration. Table IIb shows the mean values of plasma and urinary levels of AC and FC in nonseptic surgical patients and in septic patients during continous iv infusion of AC. If compared to AC and FC levels in the untreated groups (IIa), all plasma and urinary values were significantly higher during carnitine infusion ($p < 0.001$), but plasma FC in septics showed only a slight increase, of borderline significance (46 ± 26 *vs* 59 ± 26 μmol/liter; $p < 0.05$). In particular, plasma AC showed a 6-fold increase in treated nonseptics, *vs* a 4-fold increase in treated septics; plasma AC/FC ratio showed a 3-fold increase in nonseptics during treatment, *vs* a 2-fold increase in sepsis.

During carnitine infusion, we did not observe significant changes in MR, CO_2 production, O_2 consumption, or RQ in nonseptic surgical patients; however, in sepsis, CO_2 production decreased from 170 ± 42 to 143 ± 30 ml/min/m^2 ($p < 0.05$), and RQ decreased from 1.03 ± 0.18 to 0.87 ± 0.19 ($p < 0.02$) (see Table III).

Table IVb reports the mean values of glucose and lipid metabolism parameters, in nonseptics and in septics, during AC infusion. In comparison with the values in the untreated groups (IVa), plasma triglycerides were significantly lower in nonseptics during carnitine infusion ($p < 0.05$); no other significant change was observed, even though mean plasma β-hydroxybutyrate levels showed a 37% decrease in nonseptics and a 23% decrease in septics, during carnitine infusion.

The effect of AC infusion on RQ in sepsis is evident in Figure 3, where the multiple correlation between RQ, MR, and glucose calories is shown. On the same range of MR and caloric intake, in sepsis, the infusion of carnitine was associated with lower RQ; RQ = 1.28 − 0.185 (carnitine effect) − $0.25 * 10^{-3}$ (MR) + $0.063 * 10^{-3}$ (cal/BSA) $n = 34$; $r^2 = 0.62$; F = 16.1; $p < 0.001$; (cal/BSA = glucose cal/m^2/24 hr).

DISCUSSION

Our data show that septic patients on TPN are characterized by low plasma levels of short chain AC and low plasma AC/FC ratio, if compared to nonseptic surgical patients on TPN or to preoperative controls. On the other hand, as previous reports have shown,[32,33] plasma levels of *total* carnitine do not decrease during sepsis. We have already reported low plasma levels of AC during sepsis in previous preliminary studies;[34,35] low levels have also been reported in hypermetabolic states such as burns[36] and severe injury,[37] while normal to low levels have been observed in adult surgical patients during prolonged TPN, with variable degrees of stress.[38] In a recent study, a significant decrease of both FC and AC was found in day 4 after trauma, in severly injured patients on TPN.[39] Although a high intake of glucose calories might decrease plasma AC levels,[37] we do not think that this can explain the low plasma AC we observed in septic patients, since we could not find any correlation between plasma AC and infused calories; moreover, as shown in Table IIIa, the calories intake/MR ratio was lower in septics than in nonseptics.

Another relevant feature of our septic patients was the increased excretion of free carnitine. The normal excretion of total carnitine, varying with sex, age, and diet, ranges between 100 and 400 μmol/24 hr.[40–42] Increased excretion of carnitine (mainly FC) has already been reported in different stress conditions:[34,36,39,43–47] burns, surgical trauma, sepsis. Much evidence suggests that this urinary loss of FC is somehow proportional to the magnitude of injury: the higher the catabolic response of the body, the larger the amount of carnitine excreted. In severely burned patients, Cederblad et al[36] observed a significant positive correlation between the percentage surface area burned and the mean value of carnitine excretion, which was strikingly increased from day 2 through day 7 postburn. In a recent study on multiply injured patients,[43] the same authors found a significant correlation between total carnitine excretion and net nitrogen losses from days 2 through 8 after trauma, and a positive correlation between carnitine excretion and 3-methyl-histidine excretion, but only in days 6 to 8 after trauma.

Increased carnitine excretion has also been observed in starvation,[48,49] in relationship with increased lipolysis. However, in prolonged starvation lipolysis is the funda-

mental catabolic mechanism, while energy metabolism is depressed; in hypermetabolic states—and specially in sepsis—lipid oxidation is increased,[7] but at the same time there is also an increase in the oxidation of all substrates.[10] Furthermore, the increase of carnitine excretion is qualitatively different (increased urinary FC in stress, increased AC excretion in starvation), and the concomitant variations in plasma levels are different (high levels of plasma AC in starvation, but normal or low levels of plasma AC in stress).[50]

Relationship between Low Plasma AC and Septic Hypermetabolism

Our findings confirm that the metabolic response to sepsis is qualitatively different from the response to nonseptic injury.[5,18,19] In sepsis, a yet unknown metabolic stimulus causes a hypermetabolic state with increased muscle protein catabolism and increased utilization of endogenous substrates. These and other metabolic abnormalities are associated with a peculiar pattern of cardiorespiratory adaptation, which may influence the clinical course and the prognosis dramatically. Several authors have tried to correlate the adaptive cardiorespiratory response to the metabolic alterations, to provide a better understanding of the pathophysiologic mechanisms of sepsis and to support nutritional decision making in the management of these patients.[2,3]

The significant correlation between plasma levels of AC (AC/FC), a-$\bar{v}DO_2$, and free fatty acids (FFA) is a further clue to the tight links described between hemodynamic and metabolic patterns in sepsis:[1,2] septic patients with narrower a-$\bar{v}DO_2$ (more hyperdynamic) have lower AC/FC ratio and lower FFA (see Fig. 2). Although mean values of FFA are in the normal range in our septic group, it is interesting that severe sepsis (narrow a-$\bar{v}DO_2$ and low AC/FC) is associated with lower FFA levels (Fig. 2). Low plasma levels of FFA have been reported also by Askanazi and coworkers[51] in TPN-supported hypermetabolic patients. Such direct correlation between AC and FFA has already been observed during starvation,[48,50] even though within a different range of plasma values (high AC, high FFA).

The presence of a significant influence of AC/FC on a-$\bar{v}DO_2$ (direct correlation between AC/FC and a-$\bar{v}DO_2$: $F = 4.2$, $r^2 = 0.11$ of the total $r^2 = 0.53$), suggests that more hyperdynamic septics (narrower a-$\bar{v}DO_2$) have lower AC/FC. This finding agrees with the observation that in more severe sepsis (higher MR),[3] plasma levels of AC are lower (see Fig. 1).

Effects of AC Infusion

In contrast to previous reports,[7,52,53] we did not find significant difference between RQ in sepsis and RQ after nonseptic surgery (Table IIIa).

However, during the infusion of AC, the RQ decreased significantly only in septic patients (from 1.03–0.87) mostly because of decreased CO_2 production, while in nonseptic patients the decrease was not statistically significant (from 1.07 to 1.00) (Table IIIb).

Septic patients receiving carnitine infusion have lower RQ at each level of caloric intake and at any MR, if compared to untreated septics (see Fig. 4). It is interesting to notice that 10 of 12 RQ studies during carnitine infusion (ie, six patients) were performed in septic patients already studied without infusion.

It has been suggested that the hypermetabolic state of sepsis may be associated with a preferential utilization of substrates characterized by low RQ (branched-chain amino acids: average RQ = 0.54; fatty acids: RQ = 0.7); a preferential oxidation of lipid fuel in sepsis has already been shown.[7,53–56] The recent identification of branched-chain AC in muscular tissue [16] and the finding that carnitine is able to enhance the oxidation of leucine and other branched-chain amino acids[15] have stressed the role that carnitine may play not only in FFA oxidation, but also in the utilization of branched-chain amino acids into the Krebs cycle. The administration of pharmacologic amounts of AC might have enhanced the oxidation of such substrates, maybe by removing a limiting factor or by correcting a possible carnitine deficit, which is to be expected in sepsis much more than in nonseptic injury.[57,58]

It is likely that these effects of D, L-AC administration would have been more evident had we administered L-AC alone, since D-carnitine is metabolically inactive and may have an antagonist effect *vs* L-carnitine.[59] On the other hand, the infusion of carnitine in the esterified form (AC) might have facilitated the metabolic effects, since AC, if compared to the nonesterified form, can more easily diffuse in the tissues and in organic fluids, and it may have a "sparking effect" in the intracellular metabolism.[60]

However, in the present study, the administration of such a large load of AC did not eliminate the difference between sepsis and nonseptic surgery (Table IIb), since plasma levels of AC were always lower in septics even during AC infusion (25 ± 21 μmol/liter in treated septics *vs* 78 ± 40 μmol/liter in treated nonseptics, $p < 0.01$). This might possibly be explained by an increased tissue uptake of carnitine in the hypermetabolic patient.

Carnitine Supplementation during TPN

From the analysis of these data the question arises whether the administration of carnitine might be useful in some clinical situations in which TPN cannot correct metabolic failure.

Up to now, several congenital carnitine deficiency syndromes have been described,[61] but little is known about acquired deficiency of carnitine. Systemic depletion of carnitine has been detected in some clinical states associated with increased loss of carnitine (uremic patients on chronic intermittent hemodialysis)[62] or with reduced endogenous synthesis plus reduced exogenous intake, such as in cirrhosis,[63] in severe malnutrition,[44] or in premature infants receiving carnitine-free TPN.[64]

At present, carnitine is not administered during TPN. As a matter of fact, as long as the patient is not septic and does not undergo any surgical procedure,[44] urinary loss does not increase, and plasma levels may stay within the normal range even for 20 to 30 days.[38,65] It is likely that in such conditions endogenous synthesis can in-

crease and meet the requirements of the tissues, provided that the parenteral solutions contain enough lysine (precursor of carnitine synthesis).

In contrast, the patient who undergoes a surgical procedure will show increased urinary loss of carnitine, proportionally to the severity of the injury. Furthermore, if sepsis occurs, the requirement of carnitine in the peripheral tissue will eventually increase, due to an increased oxidation of carnitine-dependent substrates. In such clinical situations, we ignore whether endogenous synthesis of carnitine (usually about 100 μmol/24 hr)[46] can meet the demand. Moreover, endogenous synthesis might be impaired, even when, as in the present study, daily administration of lysine in parenteral fluids is four to five times the daily requirement for adults recommended by WHO[66] eg, if the patient is cirrhotic or severly malnourished.[44,63,67]

In clinical situations associated with prolonged increased excretion of carnitine, increased requirements, and eventually depressed synthesis, some authors have detected low carnitine concentrations in the skeletal muscle (Border et al[57] in sepsis; Bruyns et al[37] in injured patients).

Finally, in a recent report, Worthley et al[68] have described one case of carnitine depletion during TPN in a severe septic patient, in association with some metabolic abnormalities (reactive hypoglycemia and hyperbilirubinemia) which receded after treatment with L-carnitine (400 mg/24 hr), when normalization of plasma carnitine levels occurred.

CONCLUSION

The septic state is characterized by marked abnormalities in plasma and urinary levels of carnitine, low plasma levels of short-chain AC (which stay unexpectedly low even during continous infusion of pharmacologic amounts of AC), and increased urinary excretion of nonesterified carnitine, despite normal plasma levels. Although the pathogenesis of such abnormalities is still unclear, they seem to be related to the hypermetabolic-hypercatabolic state seen in this condition.

The important role of carnitine in the oxidative metabolism of the septic patient is evident during AC infusion. At any level of caloric intake, carnitine administration reduces the RQ in septics, suggesting an enhancement of the oxidation of carnitine-dependent low RQ substrates (fatty acids and branched-chain amino acids) in preference to glucose, and a reduction in the amount of glucose carbon diverted to lipogenesis.

Although further investigations are required (such as kinetic studies and evaluation of carnitine levels in the tissues), much evidence suggests the possibility of a relative or absolute deficiency of carnitine in the critically ill patient during TPN, specially in the hypermetabolic septic patient (decreased exogenous intake; increased urinary loss; eventually depressed synthesis; theoretically increased requirement in the tissues).

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