Amino Acids (1997) 12: 237–247

Amino
Acids

Proline metabolism in sepsis

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Accepted March 13, 1996

Summary. Sepsis is characterized by an abnormal increase in plasma proline (PRO) level, which tends to be related to the severity of disease. This study has been performed to assess the relationship between changes in plasma PRO and levels and doses of other amino acids (AA) in critically ill septic patients undergoing total parenteral nutrition (TPN).

Sixteen septic patients receiving TPN were randomly divided into two groups: 8 patients (Group A) received TPN with a standard AA solution, and 8 patients (Group B) with a modified AA solution (isonitrogenous, branched-chain AA enriched, with unchanged PRO concentration). Serial determinations of plasma AA profiles and of other variables were performed in each patient for a total of 396 measurements. In Group A mean plasma PRO level was 372μM/L; changes in PRO were tightly correlated with changes in the levels of most of the other AA, and the highest PRO levels characterized the more severely unbalanced septic metabolic profiles. In Group B, plasma levels of PRO and of the other AA (except glutamate, aspartate, taurine and the three branched-chain AA) decreased. The decrease in PRO level was well correlated with the increased branched-chain AA dose and with simultaneous decreases in plasma lactate and respiratory quotient. These changes could be related to a specific effect of branched-chain AA on septic metabolic derangement and on PRO metabolism, and to an improved balance between protein synthesis and catabolism.

Keywords: Amino acids – Proline – Sepsis – Lactate – Parenteral nutrition – Amino acid metabolism – Branched-chain amino acids – Respiratory quotient

Introduction

Proline (PRO) metabolism is altered in sepsis and the relevance of changes in plasma PRO in this disease has received considerable attention in the last decades. The more abnormal increases in plasma PRO have been found

associated with a greater severity of septic illness (Cerra et al., 1979a); this finding has been correlated with septic hepatic dysfunction and with a more strict dependency of PRO, compared to the other amino acids (AA), on the liver for its metabolism. However little information is available to thoroughly understand the dynamics of PRO changes and the simultaneous correlates with other AA changes and with AA doses in sepsis. Our study has been performed to assess the relationship between plasma levels of PRO and of the other AA, in septic patients undergoing total parenteral nutrition (TPN) with a standard AA formula, and the changes induced by the administration of a modified AA formula (isonitrogenous, branched-chain AA enriched) containing similar PRO doses.

Patients and methods

The study has involved the analysis of 396 AA-grams obtained in 16 severely injured post-traumatic patients who developed sepsis. Sepsis was diagnosed on the basis of a temperature greater than 101°F (38.3°C), white blood cell count greater than 12,000 or less than 3,000 cell/mm^3, demonstration of a source of infection by a positive wound, abscess, or blood culture, or by a positive sputum culture in the case of respiratory infections (Chiarla et al., 1988). No patient had oliguric renal failure. The patients were receiving total parenteral nutrition (TPN) with glucose (291 ± 69 mg/Kg/hr, mean ± SD) fat (40 ± 35 mg/Kg/hr) and mixed AA (64 ± 22 mg/Kg/hr). Randomly, 8 patients were receiving in the TPN a standard AA solution: Group A, Travasol, Clintec Nutrition, Deerfield, IL; and 8 patients a modified AA solution with a similar PRO concentration and different concentrations of other AA: Group B, 49% branched-chain AA-enriched admixture (BC), Clintec Nutrition, Deerfield, IL (Table 1). Doses of non-protein caloric sources and of total AA did not differ in Groups A and B. Groups were also similar with regard to body weight (72.9 ± 9.9 vs 75.9 ± 12.8 kg), height (174 ± 8 vs 175 ± 6 cm), BSA (1.87 ± 0.16 vs 1.91 ± 0.16 m^2) (Du Bois and Du Bois, 1916), ratio of actual to ideal body weight

Table 1. Composition of AA solutions (g/100 g)

	Group A	Group B
Alanine	20.71	12.47
Arginine	10.35	7.30
Glycine	20.70	6.34
Histidine	4.38	3.20
Isoleucine	4.77	16.67
Leucine	6.19	18.11
Lysine	5.79	3.72
Methionine	5.79	2.60
Phenylalanine	6.18	3.40
Proline	4.19	3.99
Serine	0.00	3.14
Threonine	4.18	2.94
Tryptophan	1.79	1.30
Tyrosine	0.40	0.23
Valine	4.58	14.59
Total BCAA %	15.54	49.37

(1.11 ± 0.09 vs 1.14 ± 0.18) (Metropolitan, 1984), estimated lean body mass (52.6 ± 6.6 vs 54.4 ± 5.1 Kg) (Hume, 1966), mortality rate (12.5% vs 25%), age (25 ± 6 vs 32 ± 19 yr) and sex distribution, injury severity score (medians 31 vs 30, ranges from 14 to 48 and from 11 to 54, respectively) (Greenspan et al., 1985) and sepsis severity score (medians 30 vs 28, ranges from 9 to 54 and from 11 to 51, respectively) (Stevens, 1983; Skau et al., 1985). One patient in each group died of progressive organ failure. One additional patient in group B died suddenly of myocardial infarction.

Plasma samples for AA determinations, obtained on a 8-hour basis to account for diurnal variation, were analyzed in a Beckman AA analyzer. To account better for the influence of infused AA on plasma AA profiles, also the rates of infusion of substrates were reassessed every 8 hours. Plasma clearances of AA were determined by using a previously described method (Clowes et al., 1980a, 1980b; Pearl et al., 1985; Pittiruti et al., 1985; Chiarla et al., 1988). As an additional measurement, plasma lactate was determined on a 24-hour basis together with the AA, and simultaneous arterial and mixed venous blood samples were collected for the determination of respiratory quotient (RQ) from blood gas analysis (Giovannini et al., 1993). The statistical analysis and validation of the results were performed by least-square regression analysis (Scheffé), with skewness and kurtosis control, analysis of residuals and use of a "best-fit" computer program selecting for each correlation the simplest possible regression yielding the best control of variability, based on Mallows' Cp criteria (Seber, 1977). Correlation ratio and link ratio were determined according to the method by Hjelm et al. (Hjelm et al., 1993, 1994). A correlation ratio is the ratio between the number of statistically significant correlations ($p < 0.05$) between pairs of AA and the maximum observable correlations. A link ratio is the frequency of statistically significant correlations between a particular AA and other AA.

Results

Values of plasma AA-grams in Group A and B are listed in Table 2. In Group A (TPN with standard AA solution) plasma PRO was directly correlated to the level of most of the other AA (Fig. 1). In this group, the link ratio for PRO was 0.88 and the correlation ratio for the whole 25-AA system was 0.83

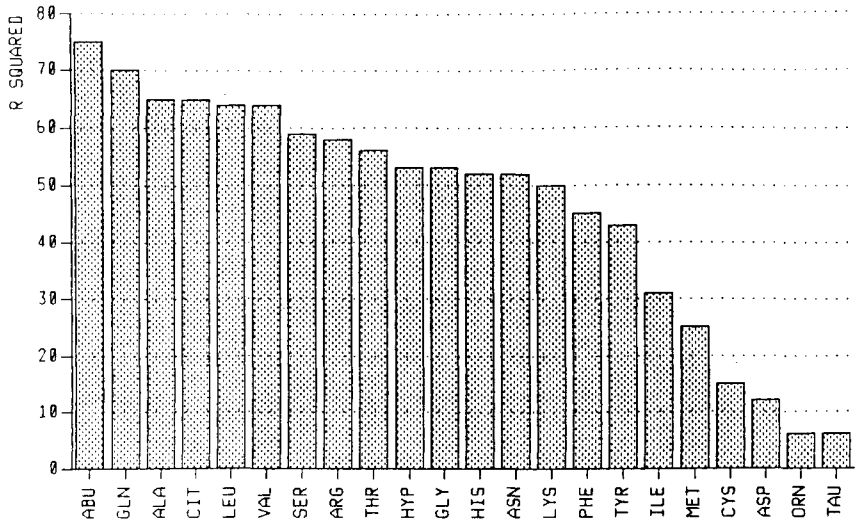

Fig. 1. Coefficients of determination (r^2s) for the direct correlations between plasma PRO and other AA levels during TPN with standard AA support. There were no significant correlations between plasma PRO and tryptophan, or glutamate ($p > 0.05$)

(Fig. 2A). The highest levels of plasma PRO (PRO > 3.0 SD from the mean value of reference control measurements, that is, PRO > 580μm/L) were associated with abnormally high levels of most of the other AA (Fig. 3, Table 3), although changes in PRO were more prominent. Plasma lactate in Group A was 1.93 ± 1.10mM/L, and RQ was 0.86 ± 0.08.

In Group B (TPN with 49%-BC solution) plasma levels of all AA (except glutamate, aspartate, taurine and the three BC) decreased and tended to vary within smaller ranges (Table 2). However the relationships between plasma PRO and the levels of most AA maintained similar directions and shapes, compared to those observed in Group A. Exceptions were the relationships between PRO and the levels of the three BC (leucine, isoleucine and valine), whose regression slopes were significantly lower in Group B compared to Group A ($p < 0.001$): that is, there were direct relationships between PRO level and each BC level in both Group A and Group B, but in Group B PRO levels were significantly lower than in Group A at any given BC level. By pooling together all measurements, it was found that these differences were significantly correlated to the administered BC doses (Table 4). The link ratio for PRO in Group B was unchanged with respect to the link ratio observed in Group A (= 0.88); the correlation ratio for the whole AA system was 0.73 (Fig. 2B).

Table 2. Plasma levels of amino acids (μM/L, mean ± SD)

	Group A (n = 227)	Group B (n = 169)
Alanine	392 ± 233	240 ± 60
α-amino-n-butyric acid	24 ± 26	8 ± 5
Arginine	114 ± 46	82 ± 25
Asparagine	76 ± 88	39 ± 14
Aspartate	9 ± 6	10 ± 12
Citrulline	17 ± 18	10 ± 3
Cystine	51 ± 24	49 ± 12
Glutamate	73 ± 49	82 ± 67
Glutamine	602 ± 468	466 ± 102
Glycine	363 ± 210	205 ± 45
Histidine	124 ± 171	69 ± 12
Hydroxyproline	18 ± 15	11 ± 4
Isoleucine	69 ± 23	117 ± 40
Leucine	130 ± 51	167 ± 48
Lysine	209 ± 86	153 ± 50
Methionine	80 ± 83	33 ± 11
Ornithine	108 ± 62	66 ± 25
Phenylalanine	148 ± 72	99 ± 29
Proline	372 ± 323	158 ± 49
Serine	122 ± 62	95 ± 77
Taurine	81 ± 53	120 ± 90
Threonine	158 ± 114	96 ± 35
Tryptophan	57 ± 14	54 ± 12
Tyrosine	70 ± 41	53 ± 11
Valine	255 ± 106	361 ± 108

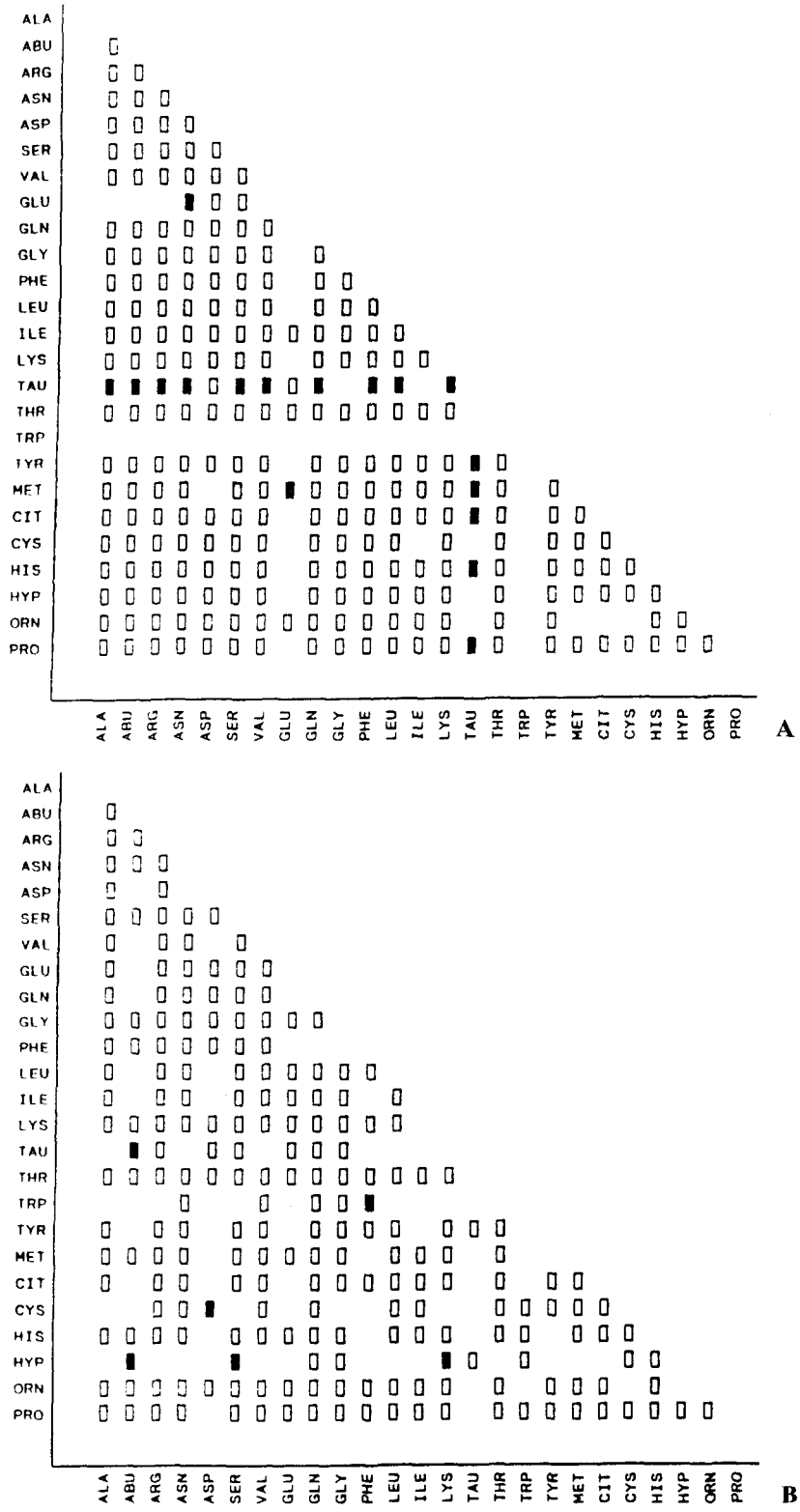

Fig. 2A,B. Simplified correlation matrices showing the statistically significant correlations ($p < 0.05$) between plasma AA levels in Groups A (**A**) and B (**B**) The matrices include also significant correlations with a relatively low r^2. Positive correlations = open symbols, negative correlations = closed symbols

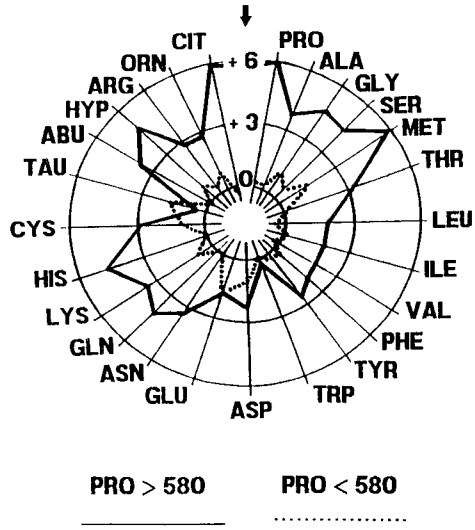

Fig. 3. Plasma amino acid levels associated with plasma PRO lower than, or higher than, 580μM/L. Units are standard deviations from the mean value of reference control measurements

Table 3. Mean ± SD of plasma AA levels (μM/L) in Group A cases with plasma PRO lower or higher than 580μM/L (see Fig. 3)

	PRO < 580μM/L (n = 185)	PRO > 580μM/L (n = 42)
Alanine	316 ± 95	732 ± 336
α-amino-n-butyric acid	15 ± 5	63 ± 40
Arginine	100 ± 29	176 ± 54
Asparagine	51 ± 34	187 ± 148
Aspartate	8 ± 5	12 ± 7
Citrulline	11 ± 5	42 ± 30
Cystine	48 ± 16	65 ± 42
Glutamate	74 ± 48	71 ± 54
Glutamine	444 ± 74	1298 ± 760
Glycine	305 ± 96	629 ± 337
Histidine	77 ± 18	332 ± 326
Hydroxyproline	14 ± 8	36 ± 24
Isoleucine	64 ± 20	94 ± 20
Leucine	113 ± 24	204 ± 70
Lysine	185 ± 54	315 ± 117
Methionine	64 ± 61	152 ± 119
Ornithine	100 ± 63	141 ± 50
Phenylalanine	128 ± 35	238 ± 115
Proline	234 ± 89	983 ± 267
Serine	103 ± 24	205 ± 100
Taurine	88 ± 55	51 ± 31
Threonine	127 ± 54	295 ± 186
Tryptophan	56 ± 15	64 ± 12
Tyrosine	61 ± 17	113 ± 76
Valine	221 ± 45	406 ± 154

Table 4. Correlations between plasma PRO levels and BCAA levels and doses ($p < 0.001$ for all regressions; $p < 0.001$ for the separate effects of BC levels and doses in each regression)

1)	$PRO_{level} = LEU_{level}\ (5.5916 - 0.2942\ LEU_{dose}) - 211.0397$ $r^2 = 0.61$
2)	$PRO_{level} = ILE_{level}\ (7.0600 - 0.5163\ ILE_{dose}) - 18.4502$ $r^2 = 0.30$
3)	$PRO_{level} = VAL_{level}\ (2.7745 - 0.1925\ VAL_{dose}) - 200.6250$ $r^2 = 0.61$

Table 5. Correlations between plasma PRO clearance and clearances or doses of BC and non-BC AA ($p < 0.001$ for all, except for regression 8)

1)	$PRO_{clear} = 0.2341\ (LEU_{clear}^{1.0640})$	$r^2 = 0.73$
2)	$PRO_{clear} = 0.2193\ (ILE_{clear}^{1.0179})$	$r^2 = 0.61$
3)	$PRO_{clear} = 0.4693\ (VAL_{clear}^{1.1173})$	$r^2 = 0.75$
4)	$PRO_{clear} = 15.5437\ (LEU_{dose}^{0.6502})$	$r^2 = 0.34$
5)	$PRO_{clear} = 23.3049\ (ILE_{dose}^{0.4737})$	$r^2 = 0.36$
6)	$PRO_{clear} = 23.6115\ (VAL_{dose}^{0.4907})$	$r^2 = 0.37$
7)	$PRO_{clear} = 9.3076\ (\text{total } BC_{dose}^{0.6107})$	$r^2 = 0.33$
8)	$PRO_{clear} = 15.6236\ (\text{total non-}BC_{dose}^{0.3056})$	$r^2 = 0.04$

Thus in Group B, compared to Group A, the mean plasma level of PRO decreased significantly (in spite of roughly equivalent PRO doses, Tables 1 and 2); and for any given leucine, isoleucine or valine level, the decrease in plasma PRO was highly significantly correlated with increases in the BC doses. A tendency to follow a similar pattern was also evident for arginine level (however arginine concentrations in the two AA solutions, and thus arginine doses in Group A and B, were not equivalent). Additional findings in Group B, compared to Group A, were a decreased plasma lactate (1.22 ± 0.37 mM/L) and RQ (0.81 ± 0.09) ($p < 0.001$).

The lower plasma PRO level at any given BC level, in patients receiving higher BC doses and roughly equivalent PRO doses, strongly suggested an increased PRO clearance associated with higher BC doses and clearances. To reconfirm this, AA clearances were also calculated (Clowes et al., 1980a, 1980b) and it was found that PRO clearance was directly and highly significantly related to the clearances of the three BC, to the BC doses ($p < 0.001$ for all, Table 5) and was practically unrelated to the non-BC AA dose.

Lactate was highly significantly correlated with PRO level (directly, $r^2 = 0.52$, $p < 0.001$) and clearance (inversely, $r^2 = 0.40$, $p < 0.001$). The correlations with the other AA levels were poorer (r^2 was 0.43 and 0.40 for the direct correlations with alanine and α-amino-n-butyric acid, respectively, and was much lower or not significant for other AA). Much poorer were also the correlations with the other AA clearances, the only exception being a direct correlation found with taurine clearance ($r^2 = 0.50$, $p < 0.001$); as taurine was not infused, this was only due to the increasing taurine levels in Group B.

It is worth mentioning, as additional information, that regression analysis performed on doses and plasma levels of each individual AA (in Group A and in Group B separately, and in both groups combined) showed that the relationships between plasma levels and doses were direct for all AA but serine. However these relationships were relatively poor for most AA ($r^2 = 0.0$ to 0.10, p inconstantly significant), except for the three BC ($r^2 = 0.20$ to 0.53, $p < 0.001$ for all).

Discussion

This study has addressed the relationship between plasma PRO and the other AA levels during TPN in sepsis, and the effect of the parenteral infusion of a modified AA formula with equivalent PRO doses.

While the plasma AA-grams obtained with the standard AA solution (Group A, Table 2) basically reconfirmed the information obtained in previous studies in sepsis (Cerra et al., 1979b, 1979c, 1980), analysis of the relationships between different AA levels has shown that PRO levels were strongly related to the levels of most of the other AA. These results demonstrate that changes in PRO levels in sepsis tend to be paralleled by similar changes in the levels of most of the other AA. Besides, the results substantiate the concept that plasma AA pool is a system (Hjelm et al., 1993, 1994) in which AA levels are tightly interrelated, and isolated changes in individual AA are quantitatively limited. Within this system, however, changes in PRO levels may become more relevant because of the metabolic peculiarities of PRO (see later). The concept of plasma AA pool as a system has been emphasized recently, together with the need of taking into account the relationships with all other AA (and the involved mechanisms) when studying the metabolism of individual AA (Hjelm et al., 1993). Related to this concept is also our finding of a simultaneous increase of most of the other AA levels in the cases with abnormally high PRO in Group A (PRO $> 580 \mu$M/L).

The plasma AA pattern of cases with the highest PRO (PRO $> 580 \mu$M/L, Figure 3) reproduces the unbalanced AA pattern which has been considered characteristic of more severe septic disease in previous studies (Cerra et al., 1979a, 1979b, 1979c, 1980); and the simultaneous larger increases of PRO, alanine, glycine, serine and methionine (all AA transported intracellularly by system "A") suggest a contribution of transport system A impairment (Guidotti et al., 1992; Hasselgren et al., 1986; Warner et al., 1987), in the presence of limited hepatic utilization of PRO (for metabolism or for protein synthesis), to plasma PRO elevation. In effect, a peculiarity of PRO is the strict dependency on the liver for its metabolism (Cerra et al., 1979a), and a role of impaired liver metabolism in determining high PRO levels in sepsis is also supported by increases in the levels of other AA (for instance, the aromatic AA phenylalanine and tyrosine) which commonly reflect abnormal liver function.

With the administration of the modified AA formula (Group B), most AA levels decreased (except glutamate, aspartate, taurine and the three BC, which increased) and tended to vary within smaller ranges (Table 2) while

their relationships with PRO maintained directions and shapes similar to those found in Group A. The exceptions were the relationships between PRO and the levels of the three BC (leucine, isoleucine and valine) which were characterized, in Group B compared to Group A, by lower PRO levels for any given BC level. This effect was significantly correlated with the increasing BC doses (Table 4) and, as mentioned in the Results and as shown in Table 5, it could be attributed to an increased PRO clearance related to the increasing doses and clearances of BC (and unrelated to the dose of non-BC AA).

Thus an explanation for the decrease in plasma PRO in Group B is provided by the BC-related increase in PRO clearance. This effect may be due to an increased utilization of PRO in protein synthesis or, in any case, to a shift in the net balance between use of PRO for protein synthesis and release of PRO from catabolism. On the other hand this is also consistent with the well-known properties of high-dose BC administration on protein metabolism (Madsen, 1982; Skeie et al., 1990) and is supported by the simultaneous decrease in plasma levels of other AA.

However, the decrease in plasma PRO in Group B might additionally be explained by a more specific effect of high-dose BC on PRO metabolism (Cerra et al., 1979a, 1980): an effect which should be paralleled by signs of improvement of the septic metabolic disregulation and should be related to the entry of BC in the oxidative cycle. This possibility is supported in our study by the reduction in RQ observed in Group B vs Group A at comparable glucose, fat and total AA doses, thus suggesting a greater BC oxidation (the RQ of BC oxidation is about 0.7) (Livesey et al., 1988). This possibility is supported as well by the reduction in lactate observed in Group B vs Group A. In fact, for a comparable glucose load and theoretical gluconeogenic load from AA (calculable for both AA solutions from Wolman et al., 1980) the lower lactate of Group B suggests a reduction of gluconeogenic flux from AA and/or an improvement in oxidative metabolism (Siegel et al., 1979), which is consistent also with the parallelism shown between lactate and alanine changes.

It must be considered, finally, that hepatic PRO metabolism is impaired (and plasma PRO increases) in the presence of high lactate levels (Marliss et al., 1972; Kowaloff et al., 1977; Kershenobich et al., 1981). Such a dependency between plasma PRO and lactate has been reconfirmed in our study by the strong correlations found between PRO level or clearance and lactate (and not found between other AA levels or clearances and lactate). A decreased inhibition of hepatic PRO metabolism, related to decreasing lactate levels, may have also contributed to the reduction in plasma PRO in Group B patients.

In conclusion these data have provided a new insight into the metabolic interactions of sepsis and the dynamics of plasma PRO changes, by quantifying the correlations between the plasma levels of PRO and of the other AA, and the relationship with AA doses. Within these interactions, the effect of high dose BC in reducing abnormally high PRO has been found to be associated with other signs of improvement of the septic metabolic disregulation: these findings may be related to the effect of BC on the balance between

protein synthesis and catabolism, or, more distinctly, on the adequacy of PRO metabolism.

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Received September 23, 1995