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BRIEF REPORT

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Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome

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Abstract *Objectives:* To describe the initial evolution of serum procalcitonin (PCT) and C-reactive protein (CRP) in previously healthy adult trauma patients and to compare the relationship of the expression of these two proteins with indicators of trauma severity.
Design: Prospective, descriptive, longitudinal study.
Setting: Surgical ICU in an university hospital.
Patients: Twenty-one patients admitted during the first posttraumatic 3 h exhibiting an Injury Severity Score (ISS) between 16 and 50 were enrolled.
Measurements: Blood sampling was performed on admission and on posttraumatic days 0.5, 1, 2 and 3 to assess serum levels of PCT and CRP. Total creatine kinase (CK_{tot}) and lactate dehydrogenase (LDH_{tot}) activities in the serum were used as tissue damage indicators.
Results: PCT exhibited an early and transient increase in serum levels similar to a more delayed change of CRP levels. Peak PCT and peak CRP were related to the ISS, the extent of tissue damage and the amount of fluid replacement during the first day. During the first 3 posttraumatic days, 90% of the patients exhibited a generalized inflammatory syndrome without infection.
Conclusions: An early and transient release of PCT into the circulation was observed after severe trauma and the amount of circulating PCT seemed proportional to the severity of tissue injury and hypovolemia, yet unrelated to infection. The predictive value of both PCT and CRP for a forthcoming multiple organ failure still remains to be clarified.

Key words C-reactive protein · Hypovolemia · Infection · Organ failure · Procalcitonin · Trauma

Introduction

Systemic inflammatory response syndrome (SIRS) is frequently encountered in surgical patients [1], making the diagnosis of infection difficult. Beside the classical bacterial examinations, simple biological parameters are desirable to facilitate a rapid diagnosis of such a complication. Serum procalcitonin (PCT) appears at the onset of medical infections and has been related to the severity and the evolution of infection [2]. The specificity of this new biological parameter has not been evaluated, especially during major non-infectious inflammatory syndromes. Because trauma is a leading cause of non-infectious SIRS, at least during the early postaggressive period [3], this study was designed (i) to describe the evolution of PCT and C-reactive protein (CRP), a classical acute phase protein [4, 5], during the initial posttraumatic phase in previously healthy adults and (ii) to compare the relationship of the early serum peaks of these two proteins with severity indicators of the posttraumatic aggression.

Table 1 Clinical and biological characteristics of the patients (CK_{tot} total creatine kinase activity, *CRP* C-reactive protein, *ISS* Injury Severity Score, LDH_{tot} total lactate dehydrogenase, *MODS* multiple organ dysfunction syndrome (if score ≥ (8), *NS* non-survivor, *PCT* procalcitonin, *S* survivor, SAPS II Simplified Acute Physiology Score II)

No.	Age	Gender	SAPS II	ISS	Early volume loading (ml)	Early SIRS	Early MODS (score)	ICU days (outcome)	Peak CK tot (U/l)	Peak LDH tot (U/l)	Peak CRP (mg/l)	Peak PCT (μg/l)
1	25	F	19	25	8,500	yes	no (0)	5 (S)	9,270	1,212	174	0.50
2	24	M	24	17	8,000	yes	no (0)	2 (S)	7,800	851	237	1.40
3	26	F	17	25	4,750	no	no (0)	5 (S)	1,190	1,347	196	2.60
4	52	F	49	27	5,400	yes	no (5)	38 (S)	504	416	187	0.60
5	22	F	16	22	6,000	yes	no (0)	7 (S)	1,520	690	146	4.60
6	29	F	24	17	3,000	no	no (2)	16 (S)	1,032	360	218	0.20
7	31	M	39	27	31,850	yes	yes (14)	28 (S)	14,207	4,246	298	1,097.00
8	47	M	18	18	6,000	yes	no (3)	10 (S)	14,029	863	29	3.50
9	28	M	45	48	30,150	yes	yes (9)	17 (NS)	5,968	1,395	216	162.00
10	26	M	40	38	7,000	yes	no (5)	46 (S)	505	533	174	0.70
11	47	F	10	29	11,250	yes	no (3)	23 (S)	2,260	501	106	1.10
12	37	M	39	29	13,500	yes	yes (8)	26 (S)	7,120	512	366	0.80
13	32	M	14	29	14,050	yes	no (1)	23 (S)	1,975	523	208	9.00
14	46	M	47	17	15,250	yes	yes (10)	31 (S)	16,000	1,240	408	2.60
15	46	M	39	38	6,900	yes	yes (8)	7 (NS)	9,827	1,993	909	6.90
16	20	F	46	20	4,050	yes	no (3)	27 (S)	551	988	223	0.60
17	20	F	28	17	4,000	yes	no (5)	7 (S)	298	485	169	1.10
18	29	F	39	41	20,500	yes	yes (11)	64 (S)	1,712	1,029	226	9.80
19	45	M	33	34	23,200	yes	no (6)	30 (S)	6,920	2,000	270	5.00
20	48	M	33	29	9,000	yes	no (0)	17 (S)	5,160	727	186	7.60
21	20	M	43	34	37,000	yes	yes (12)	4 (NS)	18,200	2,500	1,123	925.00

Methods

Study population

Trauma patients without previous chronic disease who were admitted to our Surgical ICU between January 1, 1996 and April 30, 1996, were included in the study if the following criteria were met: (1) delay between trauma and admission of 3 h or less, (2) Injury Severity Score (ISS) above 16 and below 50 [6], (3) age between 18 and 55 years and (4) creatinine plasma level of 100 μmol/l or less. The study was approved by the local Ethics Committee and care of the patients was directed by the same existing protocols. Volume loading was carried out to obtain a mean arterial pressure of 70 mm Hg or more, hemoglobin of 10 g/dl or above, equivalent prothrombin time of 40% or more and platelet count of 75 giga/l or above. The total amount of fluids infused during the first 24 h ('early volume loading') was noted as an indicator of hypovolemic challenge. The Simplified Acute Physiology Score (SAPS II) was calculated on admission [7]. Clinical evaluations were carried out without the results of CRP and PCT being known. Each day, patients were classified as exhibiting 'SIRS' or 'sepsis' according to the previously proposed definitions [8] and a score of multiple organ dysfunction syndrome (MODS) specifically designed for the trauma patient was calculated on days 2 and 3 [3]. Each patient was examined daily for the presence of infection until day 5. Blood cultures (t.i.d.) and urine cultures (twice a week) were systematically carried out from patients exhibiting SIRS, and specific bacteriological examinations were performed when indicated. Bacterial infections were defined according to the criteria of the Centers for Disease Control [9].

Laboratory procedures

Blood sampling for determination in duplicate of tissue injury indicators and inflammatory parameters was performed on admission and on posttraumatic days 0.5, 1, 2, and 3. The tissue injury indicators consisted of total creatine kinase activity (CK_{tot}) for specific muscle injury and total lactate dehydrogenase activity (LDH_{tot}) for non-specific tissue injury [10] with values in healthy subjects less than 270 U/l and 420 U/l, respectively; CK_{tot} and LDH_{tot} were assessed by measurement of the catalytic concentrations of enzymes at 37 °C according to the recommendations on IFCC methods. Inflammatory parameters comprised serum levels of CRP and PCT. CRP was measured by rate nephelometry immunoassay with a Beckman Array System (Beckman instruments, Gagny, France) using 200 μl of serum. Inter- and intra-assay variations at both low (5 mg/l) and high (120 mg/l) concentrations were less than 8% and 5%, respectively. With this assay, serum levels of CRP in healthy adults were less than 12 mg/l. Using 20 μl of serum, PCT was measured by an immunoluminometric assay (LUMItest PCT, Brahms Diagnostica, Berlin, Germany) whose detection limit was 0.01 μg/l. Inter- and intra-assay variations at both low (0.01 μg/l) and high (500 μg/l) concentrations were less than 8% and 7%, respectively. With this assay, serum levels of PCT in healthy adults were less than 0.1 μg/l.

Analysis of data

The results are expressed as medians and total ranges. A phenomenon was defined as 'early' if it was present during the first 3 days posttrauma. Relationships between clinical findings and biological results were assessed using a Spearman rank correlation. A p value below 0.05 was considered to be significant.

Results

Twenty-one patients were included in the study (Table 1). There were 12 male and 9 female patients, aged 29 years (20–52), and admitted for a median length of

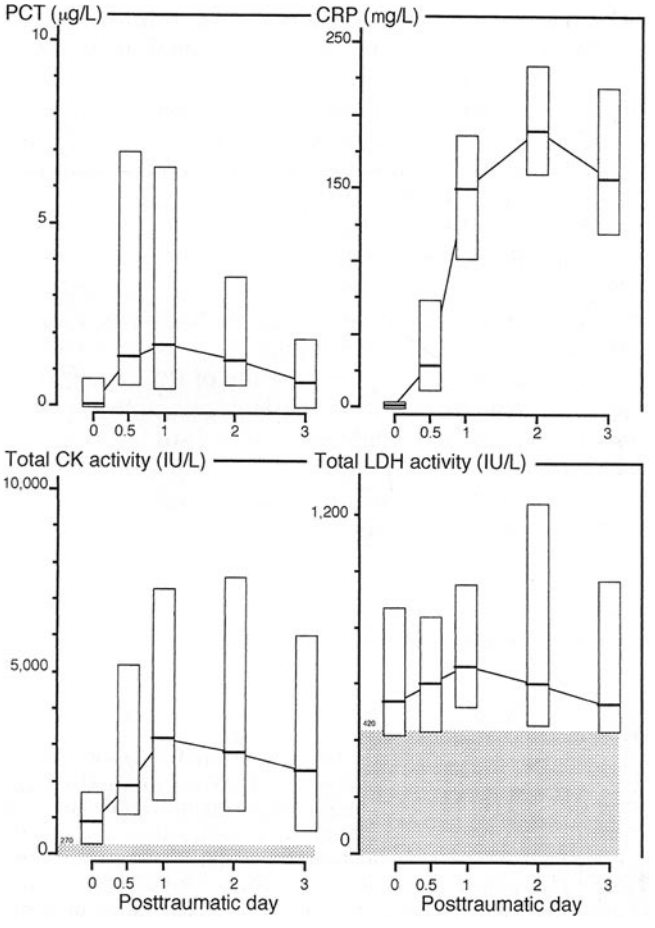

Fig. 1 Evolution of procalcitonin (PCT) and C-reactive protein (CRP) serum levels, total creatine kinase (CK_{tot} and lactate dehydrogenase (LDH_{tot}) serum activities during the first 3 posttraumatic days in 21 patients. Results are depicted as median *(bold horizontal line)* and 25th–75th percentiles *(box); hatched areas* represent normal values

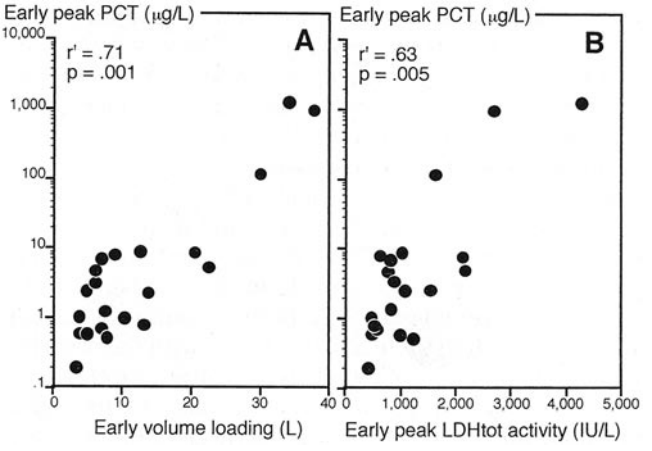

Fig. 2 Relationships between the early (i.e., within first 3 days posttrauma) peak of serum procalcitonin (PCT) concentration and volume replacement during the first (**A**) and the early peak of lactate dehydrogenase activity (LDH_{tot}) (**B**), respectively

ICU stay of 17 days (2–64). Patients suffered from a severe blunt trauma [ISS = 27 (17–48)] with impaired physiological condition [SAPS II = 33 (10–49)], hypovolemia [early volume loading = 8,000 ml (3,000–37,000)] and rhabdomyolysis [early peak CK_{tot} = 5,160 U/l (298–18,200)] (Table 1). These was a 14% ICU mortality.

During the first 3 days, 19 patients (90%) exhibited SIRS and 7 of them had MODS (33%) without any definite signs of infection (Table 1). The functions involved in the process were brain (6/7), heart and vessels (5/7), lungs (5/7), blood (3/7), metabolism (3/7) and liver (2/7). Peak serum PCT was above the usual threshold in all patients and demonstrated a huge increase in three of them, since the concentration exceeded 150 µg/l (Table 1). The elevations of all parameters were transient, with a median peak level of PCT, CK_{tot} and LDH_{tot} on the first posttraumatic day, whereas CPT peaked on the second day posttrauma (Fig. 1). A significant relationship existed between the early peak of PCT and injury severity ($r = 0.050$, $p = 0.025$), early volume loading ($r = 0.71$, $p = 0.001$, Fig. 2) and tissue damage [peak CK_{tot} ($r = 0.048$, $p = 0.031$) and peak LDH_{tot} ($r = 0.063$, $p = 0.005$, Fig. 2)]. A similar relationship was also demonstrated for early volume loading ($r = 0.50$, $p = 0.025$), tissue damage [peak CK_{tot} ($r = 0.50$, $p = 0.024$) and peak LDH_{tot} ($r = 0.054$, $p = 0.016$)] and the early peak of CRP. The peak PCT level was significantly higher in patients developing subsequent MODS ($p = 0.015$, Mann Whitney U-test, Table 1). The same held true for the peak CRP level ($p = 0.001$).

Discussion

Postinjury MODS is usually described as a bimodal phenomenon [3]. During the first 3 posttraumatic days, organ dysfunction seems to be mainly influenced by the direct sequelae of tissue damage and shock through the release of inflammatory mediators without evidence of infection [5], whereas a less severe trauma insult can create an inflammatory environment such that a later, otherwise inocuous, secondary inflammatory insult (e.g., surgical procedure or infection) precipitates severe SIRS and MODS [3, 11]. This well-known evolution of inflammation during the early postaggressive phase explains the time limitation of the present study.

During the study period, the vast majority of the patients exhibited SIRS and an increase in serum CRP correlated with the trauma severity. Severe injury produces rapid and large increases in circulating concentrations of interleukin (IL)-6) and IL-8 whereas endotoxin, IL-1

and tumor necrosis factor α (TNFα) were not found [12, 13]. IL-6 stimulates the production of acute-phase proteins and serum CRP is increased for at least 2 weeks after uncomplicated surgery or trauma, even in the absence of organ failure or sepsis [5, 14].

In healthy subjects, endotoxin injection resulted in a rapid (3–4 h) and sustained (at least 24 h) increase in serum PCT concentration [15]. TNFα and IL-6 peaked before the appearance of PCT in plasma suggesting that these cytokines may play a role in the release of PCT from putative target cells [15]. In the patients the serum PCT concentration seemed to correlate with the severity of bacterial infection and was lowered by antibiotic treatment [2]. From the present results, PCT also seems to be a pertinent indicator of the non-infectious inflammatory challenge, because its serum levels correlated with the extent of tissue injury depicted by ISS and the lactate dehydrogenase activity [10] and with the massive early volume replacement, reflecting the severity of hypovolemic shock. Indeed, increased serum PCT was reported in patients with burns-related inflammation without evidence of acute infection [2]. Furthermore the hypercalcitoninemia recently reported in uncomplicated trauma patients [16, 17] may, in fact, represent a secretion of PCT, because the assay methodology used for determination of calcitonin levels (RIA) would not exclude cross-reactivity with PCT in these studies. Since a fall in calcium concentration is frequently observed during inflammatory processes and usually results in an inhibition of calcitonin production, it is unlikely that calcemia had a role in triggering PCT secretion after trauma.

In conclusion, an early production of PCT after trauma seems to be related to tissue damage and the magnitude of hypovolemic challenge. Further studies are warranted to identify the site of production and the role of PCT as a predictor of forthcoming multiple organ failure with or without sepsis.

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