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Host Defense Dysfunction in Trauma, Shock and Sepsis

Mechanisms and Therapeutic Approaches

With 416 Figures and 153 Tables

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Diagnostic Role of New Mediators and Markers of Inflammation in Multiple Injured Patients

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Introduction

The major cause of late death after severe blunt trauma is (multiple) organ failure (OF), which is a direct consequence of mediators released during primary tissue damage and circulatory shock. To further elucidate the role of inflammatory mediators in the development of OF we performed a prospective study in severely injured patients. In a second step we examined the early prognostic value of objective biochemical markers for death and the development of OF compared to the Injury Severity Score (ISS).

Patients and Methods

In the period 1986–1989, traumatized patients arriving at our emergency room were included in the prospective study if all of the following criteria were met: (a) severe injuries of at least two body regions (head/brain, thorax, abdomen, skeletal system) or three major fractures, (b) age between 16 and 70 years, and (c) less than 6 h between accident and admission to the emergency department. A total of 69 primary surviving patients entered the study. The mean ISS was 36 (range, 13–66). Between days 4 and 28, 11 patients died (median survival time, 19, days). Of survivors, 29 suffered from OF, and 29 had an event-free recovery. Three groups were formed: group 1, lethal OF ($n = 11$); group 2, reversible OF ($n = 29$); group 3, no OF ($n = 29$).

Laboratory testing and recording of clinical data was started within 30 min after arrival of the patient in the emergency department and continued on a 6-h basis. After 48 h the interval was extended to 24 h for a period of 14 days. After 2

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weeks the clinical course was recorded until either transfer to a general ward or death. The biochemical markers studies are shown in the Fig. 1.

The following definitions were used:

Respiratory failure: need of mechanical ventilation and $pO_2/FiO_2 \leq 280$ or positive end-expiratory pressure ≥ 8 mmHg for at least 24 h

Renal failure: creatinine ≥ 177 µmol/l for at least 48 h

Liver failure: bilirubin ≥ 51 µmol/l for at least 48 h

Disseminated intravascular coagulation: (a) thrombocytes $\leq 100 \times 10^9$/l or fall of $\geq 30\%$ in 24 n, (b) partial thromboplastin time ≥ 50 s for 24 h, (c) 22 reptilase time ≥ 22 s for 24 h

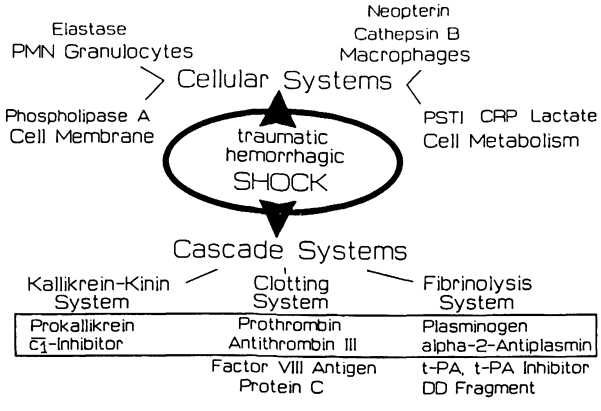

Fig. 1. Biochemical markers in traumatic hemorrhagic shock

Table 1. Complications ($n = 69$)

	Incidence (n)
Multiple organ failure	29
Sepsis	20
Respiratory Failure	42
Adult respiratory distress syndrome	17
Liver failure	42
Renal failure	17
Gastrointestinal failure	7
Disseminated intravascular coagulation	7
No complications	32

GI failure: endoscopically confirmed ulceration with bleeding, acalculous cholecystitis

MultipleOF: Failure of two or more organ systems at the same time

The complications of the 69 patients are shown in Table 1.

Statistical testing was done with the non parametric Wilcoxon test for two samples. Differences were considered significant with p values below 0.05.

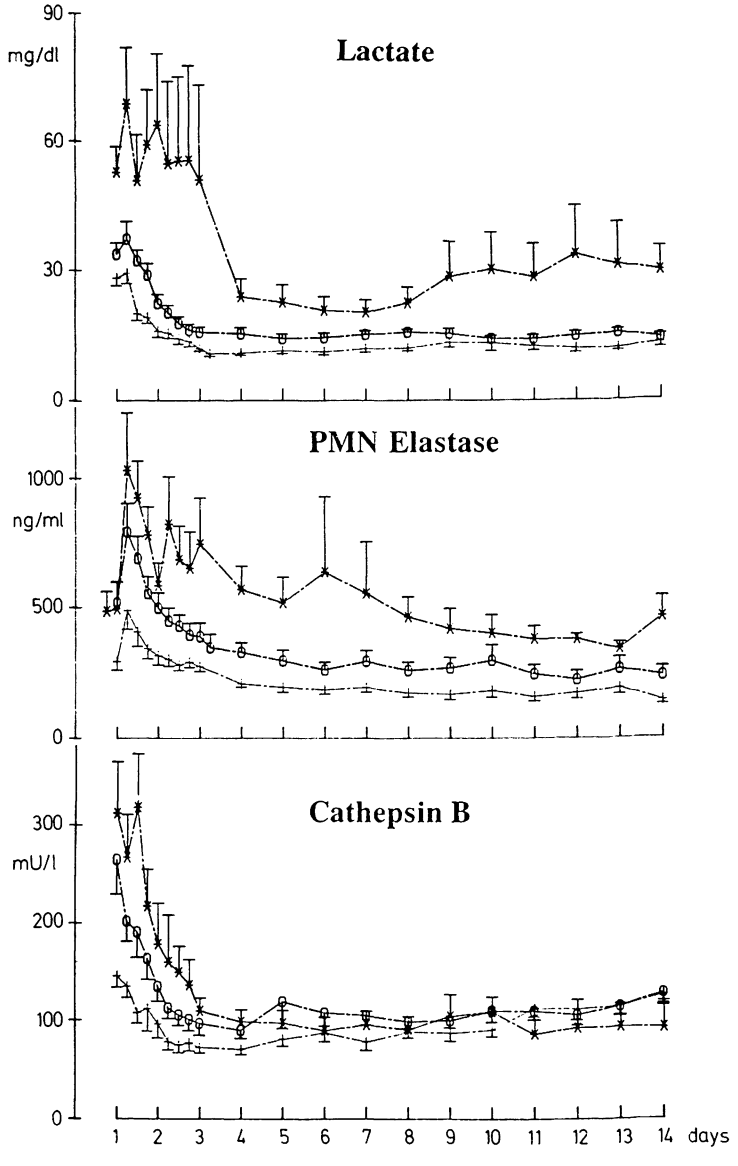

Fig. 2. Lactate, PMN elastase, and cathepsin B in groups 1 (*), 2 (○), and 3 (+)

Results

The release of mediators and indicators of inflammatory reactions in the three outcome groups is displayed in Figs. 2–4 for those markers which showed clinical relevance. The following differences proved to be significant. A higher

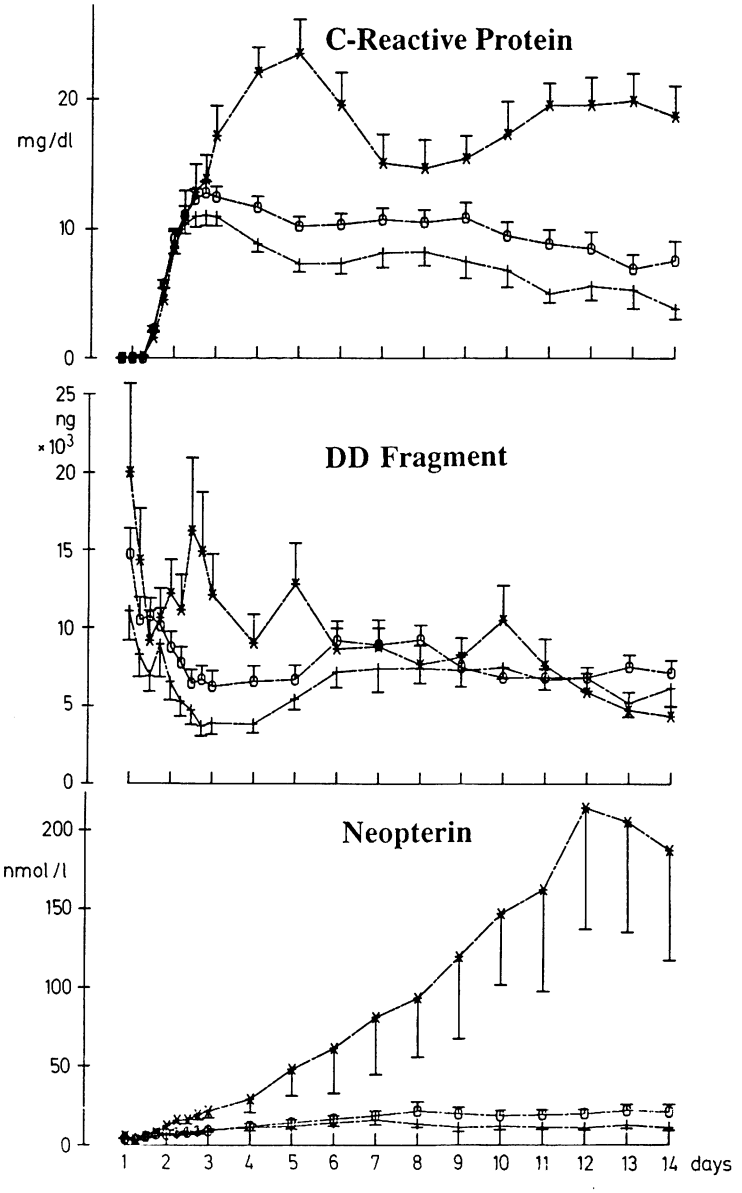

Fig. 3. C-reactive protein, DD fragment, and neopterin in groups 1 (*), 2 (○), and 3 (+)

accumulation of lactate (Fig. 3) was observed in non survivors (group 1) compared to survivors with organ failure (group 2) throughout 14 days of observation. The level of polymorphonuclear leukocyte (PMN) elastase (Fig. 2) showed a highly significant difference in groups 1 and 2 versus group 3 throughout the whole observation period and in group 1 versus group 2 after the

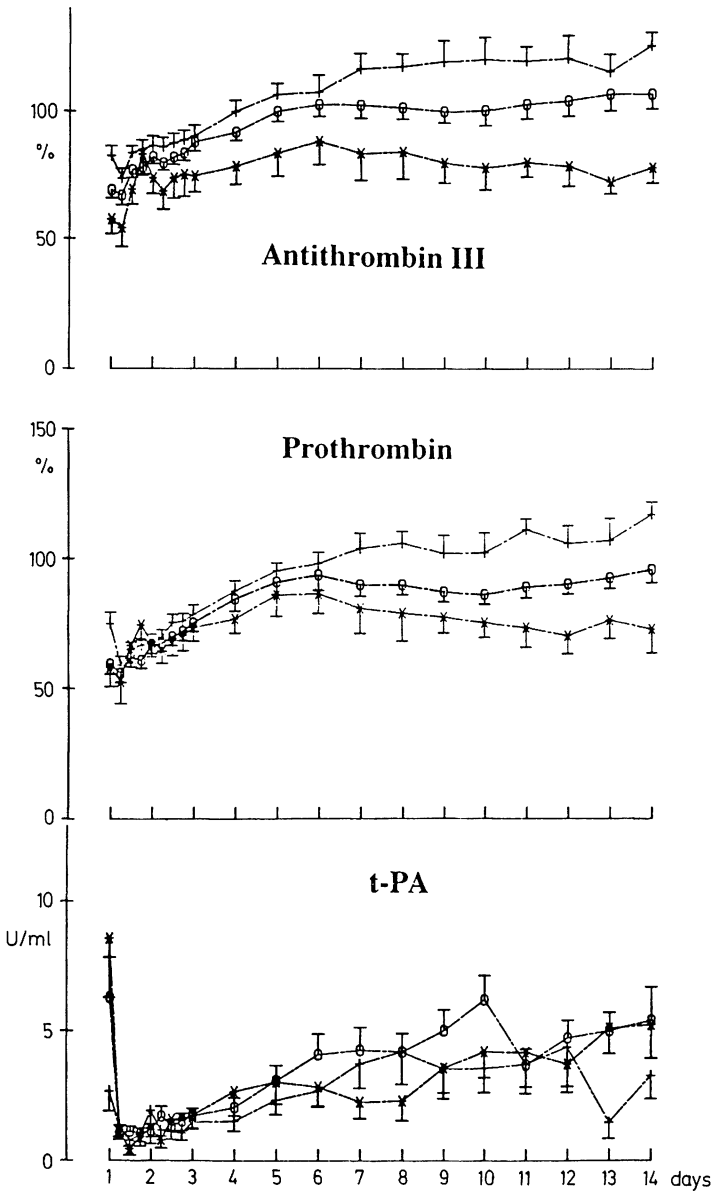

Fig. 4. Antithrombin III, prothrombin, and t-PA in groups 1 (*), 2 (○), and 3 (+)

3rd day. Cathepsin B (Fig. 2) distinguished patients with OF (groups 1 and 2) from those with uneventful recovery (group 3) within the first 4 days. The production of C-reactive protein; (CRP; Fig 3) was different among all outcome groups starting on the 3rd day after trauma. The D-dimer fragment (Fig. 3) of group 3 differed from that of groups 1 and 2 at arrival, and the levels of all three groups differed between days 3 and 5. Neopterin (Fig. 3) was higher in group 1 (nonsurvivors) compared to survivors (groups 2 and 3) from the 2nd day onwards and between groups 2 versus 3 after the 4th posttraumatic day. Antithrombin III (Fig. 4) showed a lower inhibitory activity in groups 1 and 2 versus group 3 all the time and between groups 1 and 2 (nonsurvivors versus survivors with OF) after the 1st week. At arrival, prothrombin and tissue plasminogen activator (t-PA; Fig 4) distinguished between patients devoloping OF (groups 1 and 2) and those having an uneventful recovery (group 3). In the 2nd week prothrombin differed between survivors and nonsurvivors.

As OF often started on the 1 day, prediction of later OF was possible at hospital arrival, whereas a lethal outcome could be predicted within the first 3 days. The demonstrated mediators showed a reasonable accuracy in predicting OF and death with a higher validity than the ISS Table 2. The combination of the four factors with prognostic value for death (PMN elastase, CRP,

Table 2. Prognostic value for lethal outcome at hospital arrival[a] and at day 4

	ACC	Sens	Spec	PPV	NPV
Lactate[a] (> 45 mg/dl)	88%	60%	93%	60%	93%
Elastase (> 500 ng/ml)	90%	73%	93%	67%	95%
CRP (> 20 mg/dl)	88%	67%	98%	86%	95%
Neopterin (> nmol/l)	86%	75%	93%	67%	95%
ISS (> 50)	80%	36%	88%	36%	88%

ACC, Accuracy; Sens, sensitivity; Spec, specifity; PPV, positive, predicitive value; NPV, negative predictive value.
[a]Prognostic value at hospital arrival for lactate only.

Table 3. Prognostic value for organ failure at hospital arrival

	ACC	Sens	Spec	PPV	NPV
Cathepsin B (> 190 U/l)	90%	63%	86%	86%	62%
Elastase (> 200 ng/ml)	67%	84%	42%	68%	65%
Antithrombin III(< 80%)	66%	71%	58%	71%	58%
Prothrombin (< 70%)	61%	71%	60%	73%	58%
D-dimer fragment (> 12 000 ng/ml)	61%	62%	61%	70%	52%
t-PA (> 8 ng/ml)	57%	62%	54%	68%	48%
ISS (> 30)	61%	70%	48%	65%	54%

ACC, Accuracy; Sens, sensitivity; Spec, specifity; PPV, positive, predicitive value; NPV, negative predictive value,

Table 4. Prognostic value of the combination of four parameters for lethal outcome: elastase, CRP, neopterin, lactate

	(minimum of pathological factors)		
	3	2	1
Sensitivity	53%	73%	93%
Specifity	99%	87%	67%
PPV	89%	50%	34%
NPV	92%	95%	98%
Accuracy	92%	85%	61%

PPV, Positive predictive value; NPV, negative predicitve value.

neopterin, lactate) further improved the accuracy of prediction. More than three pathological results showed a very high risk of death; normal release of all mediators indicated survival (Table 3, 4).

Summary

Biochemical mediators showed a significant difference between traumatized patients with lethal, reversible, and no organ failure. These objective parameters of inflammation might give a more accurate description of injury severity and allow a better estimation of risk for OF than many trauma severity scores.