

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/22307>

Please be advised that this information was generated on 2022-08-22 and may be subject to change.

Inflammatory mediators in relation to the development of multiple organ failure in patients after severe blunt trauma

Rudi M. H. Roumen, MD, PhD; Heinz Redl, PhD; Günther Schlag, MD; Gertrud Zilow, MD; Wolfgang Sandtner, MD; Wolfgang Koller, MD; Thijs Hendriks, PhD; R. Jan A. Goris, MD, PhD

Objective: To evaluate the posttraumatic course of several inflammatory mediators or markers (complement components C3, C3a, terminal complement complex, thromboxane B₂, C-reactive protein, elastase, and neopterin) in relation to the development of multiple organ failure and mortality.

Design: Prospective study of a selected patient group.

Setting: Surgical intensive care units in three European trauma hospitals.

Patients: Patients (n = 56) with severe blunt trauma (Injury Severity Score of ≥ 33).

Interventions: Arterial blood samples were sequentially obtained.

Measurements and Main Results: Non-survivors (n = 8) had significantly higher circulating C3a and elastase concentrations on the first postinjury day, compared with survivors (n = 48). No differences between these groups were found for terminal complement complex, thromboxane B₂, C-reactive protein, and the neopterin/creatinine ratio.

Five patients died before day 5. Eighteen patients developed multiple organ failure, which was diagnosed from day 5 onward, leaving 33 patients without multiple organ failure. The patients with subsequent multiple organ failure showed significantly higher mean circulating concentrations of C3a (914 ± 190 [SEM] ng/

mL), terminal complement complex (57 ± 17 U/mL), and thromboxane B₂ (275 ± 37 pg/mL) at the first postinjury day than the patients without multiple organ failure (566 ± 110 ng/mL, 27 ± 2 U/mL, and 169 ± 14 pg/mL, respectively). In patients with multiple organ failure, elastase concentrations were significantly higher on days 2, 3, 4, and 5 postinjury. Neopterin/creatinine ratios, on the other hand, were significantly higher in patients with multiple organ failure when the multiple organ failure had already become established (on days 8 and 10).

Conclusion: In multiple trauma patients, excessive triggering of the inflammatory cascade—as expressed by complement activation and stimulation of neutrophils producing elastase—plays an important and early role in the development of multiple organ failure. (Crit Care Med 1995; 23:474–480)

KEY WORDS: complement proteins; thromboxane; C-reactive protein; neopterin; multiple trauma; multiple organ failure; critical illness; inflammation; neutrophils; adult respiratory distress syndrome

Death after multiple trauma occurs either immediately at the scene of the accident, or within hours after the event when patients are hospitalized (1). These fatalities are mainly due to the severity of injury or to direct complications from the primary injury. A third possibility is late death after days or even weeks, because of complications in remote organ systems not necessarily affected by the primary trauma. In the latter group, most patients die of adult respiratory distress syndrome (ARDS) and multiple organ failure syndromes that are thought to have one common pathophysiologic background (2, 3). This group is of special interest, not only because of the effect that these patients have on intensive care unit (ICU) utilization, but also because the mechanisms leading to ARDS/multiple organ failure and subsequent death are unclear.

From the Department of General Surgery (Drs. Roumen, Hendriks, and Goris), University Hospital Nijmegen, Nijmegen, The Netherlands; the Ludwig Boltzmann Institute for Experimental and Clinical Traumatology (Drs. Redl and Schlag), Vienna, Austria; Institute of Immunology (Dr. Zilow), University of Heidelberg, Heidelberg, FRG; the Department of Anaesthesia and Intensive Care (Dr. Sandtner), Lorenz Böhler Hospital, Vienna, Austria; and the Department of Anaesthesia and Intensive Care Medicine (Dr. Koller), University of Innsbruck, Innsbruck, Austria.

This study was supported, in part, by a grant from the Lorenz Böhler Foundation.

In multiple trauma patients, head injury accounts for ~50% of deaths; hemorrhage accounts for ~10% to 15% of deaths; and ARDS, multiple organ failure, and sepsis account for ~30% to 35% of deaths (4, 5). The occurrence rate of multiple organ failure after multiple trauma varies from 21% to 47% (4–7) and the mortality rate within this group varies from 20% to 30%, depending on the patient populations studied and definitions used. Unfortunately, there is still no general consensus about the definition of this syndrome. Therefore, conclusions of various reports are difficult to compare and can lead to contradictory findings.

It remains puzzling why, in two patients with equivalent preexisting conditions and similar trauma and treatment, one patient recovers within a few days and the other patient develops ARDS and multiple organ failure and subsequently dies. One hypothesis on this paradigm is that a varying inflammatory reaction to trauma may lead to a sequential autodestructive process in various organ systems (2).

The present study on multiple trauma patients was performed to investigate the role of mediators and markers of the inflammatory cascades in relation to the development of multiple organ failure and mortality. The following parts of the inflammatory cascades were studied: complement activation; acute-phase protein synthesis; thromboxane production; and neutrophil and macrophage activation.

Complement Activation. Complement activation plays a central role in the inflammatory cascade, because of the release of anaphylatoxins that trigger a series of other biological events (8).

C3 is the initial key component that is activated either by the classical or the alternative pathway, the latter being the main route after trauma (8). From the activated split products, we chose C3a for measurement, because other products are more rapidly cleared from the circulation (9). C3a and its ratio with C3 (C3a/C3) has been shown to correlate positively with outcome in patients after trauma or septic shock (8–10). In addition, we measured the terminal complement complex, which is a complex formed by C5b, C6, C7, C8, and C9 and which indicates the activation of the terminal complement pathway (11). Since the generation of terminal complement complex requires activation of C5 to C5a and C5b, the terminal complement complex can be used as an indirect indicator of C5a formation (12).

C-Reactive Protein. The acute-phase reaction is a general and nonspecific response to most forms of infective and noninfective inflammatory processes, trauma, tissue necrosis, and neoplasms (13). C-reactive protein is a fast-reacting, acute-phase protein,

synthesized by hepatocytes under the influence of humoral mediators, such as prostaglandin E₁ or, especially, interleukin-6 (14). C-reactive protein may play a vital role as an opsonic protein in the immediate postinjury period, when complement is consumed (15). C-reactive protein probably acts primarily as a protective mechanism, but in some circumstances, C-reactive protein may also initiate or exacerbate inflammatory lesions (13). Some studies (16, 17) showed a positive correlation between the severity of (surgical) trauma and concentrations of C-reactive protein.

Thromboxane B₂. Eicosanoids, with a broad spectrum of biological activities, represent a class of lipid mediators that are derived from polyunsaturated fatty acids (18). The major natural source is arachidonic acid. Enzymatic catalyzation of arachidonic acid leads to either prostaglandins and thromboxanes by the cyclooxygenase pathway, or to leukotrienes by the lipoxygenase pathway. In the present study, thromboxane B₂—which is the inactive metabolite of the main biologically active product thromboxane A₂, with strong vasoactive and platelet-stimulatory effects (18)—was chosen for evaluation of the cyclooxygenase pathway. Many different inflammatory triggers (e.g., allergic reactions, toxic oxygen radicals, endotoxin) and especially septic or circulatory shock are associated with enhanced eicosanoid formation (18, 19).

Elastase. There is much evidence that neutrophils play a major part in triggering complications in septic or posttraumatic patients (6, 9). The enzyme elastase is released from stimulated neutrophils at the site of injury, infection, or inflammation and can cause tissue damage and subsequent organ dysfunction. By measuring the complex of elastase with its inhibitor α_1 -proteinase (elastase- α_1 proteinase inhibitor complex) in plasma, the degree of neutrophil activation can be quantified (20, 21).

Neopterin. There is increasing evidence that activated macrophages play a key role in the autodestructive inflammatory response to traumatic or septic events (3). After immune stimulation (e.g., by endotoxin or γ -interferon activated macrophages produce and excrete the inactive metabolite neopterin (22). Neopterin is cleared from the circulation in a creatinine-like manner and can be measured in blood as well as in urine (23, 24). To correct for possible renal insufficiency, we therefore used the neopterin/creatinine ratio to grade macrophage activation.

MATERIALS AND METHODS

During a 2-yr period, data from 56 multiple trauma patients were prospectively collected as part of a

multicenter trial on the evaluation of inflammatory mediators and scoring systems (25). Patients with blunt trauma were admitted to three trauma hospitals in Europe (University Hospital, Innsbruck, Austria; University Hospital, Nijmegen, The Netherlands; Lorenz Böhler Hospital, Vienna, Austria). Patients were included in the study if the Injury Severity Score (26) calculated from the Hospital Trauma Index (27) was ≥ 33 , which represents at least two severe lesions in different body regions or one severe and two major lesions in three different regions.

Extensive data collection was performed on hospital admission to the hospital and daily during the ICU admission, for ≤ 2 wks after injury. Informed consent was obtained from the patients' relatives before the study, which was approved by the local Ethics Committees.

Blood sampling at the ICU was done daily in the first week and every other day in the second week. Biochemical measurements were performed using the following techniques. C3a was determined by enzyme-linked immunosorbent assay technique, according to Zilow et al (28). C3 was determined by radioimmunoassay (NOR-Partigen, Behring Diagnostics, Marburg, FRG) and terminal complement complex, according to Deppisch et al (29). C-reactive protein was determined by an immunoturbidometric assay (Orion Diagnostica, Espoo, Finland). Thromboxane B_2 was determined by radioimmunoassay, as described by Flynn et al (30). Elastase- α_1 proteinase inhibitor complex was determined by enzyme-linked immunosorbent assay (Merck, Darmstadt, FRG). Neopterin was determined using a radioimmunoassay (Henning, Berlin, FRG), with neopterin/creatinine ratios expressed as $\mu\text{mol/mol}$.

Multiple organ failure and mortality rate were the focus of our inflammatory mediator study. Survivors were defined as patients discharged from the hospital alive; nonsurvivors were patients who died in the hospital because of any posttraumatic complication.

For all patients, Acute Physiology and Chronic Health Evaluation II score (31) and multiple organ failure score (2, 32) were calculated daily. For determination of the multiple organ failure score and Acute Physiology and Chronic Health Evaluation II score, the most deranged values of the various contributing parameters of each day were used.

The multiple organ failure score, according to Goris et al. (2), grades organ function as normal (0 point), moderately disturbed (1 point), or severely disturbed (2 points), with a maximum of 14 points in seven main organ systems (Table 1). Multiple organ failure was defined as an average multiple organ failure score of ≥ 4 from day 5 to day 14 (25). Statistical analyses were

Table 1. Multiple organ failure (MOF) score. MOF score is total of seven organ failure scores, with a maximum of 14 points

Organ System	MOF Score	
	1	2
Pulmonary	Mech. ventilation with PEEP ≤ 10 cm H_2O , $F_{iO_2} \leq 0.4$	Mech. ventilation with PEEP > 10 cm H_2O , $F_{iO_2} > 0.4$
Cardiac	Hypotension > 100 mm Hg; dopamine ≤ 10 $\mu\text{g/kg/min}$; nitroglycerin ≤ 20 $\mu\text{g/kg/min}$	Hypotension ≤ 100 mm Hg; dopamine > 10 $\mu\text{g/kg/min}$; nitroglycerin > 20 $\mu\text{g/kg/min}$
Renal	Serum creatinine ≥ 2 mg/dL (≥ 176.8 $\mu\text{mol/L}$)	Dialysis
Hepatic	Serum bilirubin ≥ 2 mg/dL (≥ 34.2 $\mu\text{mol/L}$) or SGOT ≥ 25 U/L	Serum bilirubin ≥ 6 mg/dL (≥ 102.6 $\mu\text{mol/L}$) or SGOT ≥ 50 U/L
Hematologic	Platelets $< 50 \times 10^9$ cells/L and/or WBCs $\geq 30 \times 10^9$ cells/L	Disseminated intravascular coagulation; WBCs $< 2.5 \times 10^9$ cells/L or $\geq 60 \times 10^9$ cells/L
GI	Acalculous cholecystitis Stress ulcer	Perforated gallbladder Bleeding from ulcer > 2 units of blood/24 hrs; necrotizing enterocolitis; pancreatitis
Central nervous	Diminished responsiveness	Severely disturbed responsiveness and/or diffuse neuropathy

MOF Score 0, no failure; MOF Score 1, moderate failure; MOF Score 2, severe failure; mech., mechanical; PEEP, positive end-expiratory pressure; SGOT, serum glutamic-oxaloacetic transaminase; WBCs, white blood cells; GI, gastrointestinal.

performed using the Wilcoxon two-sample test for comparison between groups. A $p < .05$ was considered significant.

RESULTS

Fifty-six patients entered the study (ten female and 46 male). The mean age was 33 yrs (range 14 to 71). The mean Injury Severity Score of all patients was 46 ± 10 (SD) (range 33 to 75). The mortality rate was 14%, as eight patients died. Table 2 shows the cause of death and the day after admission that these patients died. Mean Injury Severity Score of survivors was 44 ± 10 ; the mean Injury Severity Score of nonsurvivors was 55 ± 10 ($p < .01$). Because five patients died early (within 3 days), we only provide data concerning inflammatory mediators in relation to the mortality rate of the first day of admission. Differences between survivors and nonsurvivors for the various mediators are shown in Table 3. On day 1, only complement activation (expressed by C3a/C3 ratios) and elastase

Table 2. Injury severity scores (ISS), cause, and day of death in the eight patients who died

Patient	ISS	Day	Cause
1	50	1	Severe thoracic injury, ruptured lungs
2	38	3	Brain death
3	75	3	Severe thoracic injury and brain death
4	57	3	Brain death
5	57	3	Coagulopathy, ARDS + acute renal failure (early MOF)
6	57	6	Acute renal failure and brain death
7	50	9	MOF
8	57	37	MOF

ARDS, adult respiratory distress syndrome; MOF, multiple organ failure.

Table 3. Inflammatory mediators (mean \pm SD) in survivors (n = 48) and nonsurvivors (n = 8), as determined on the first day after injury

Mediator	Survivors	Nonsurvivors	p Value
C3 (mg/mL)	0.67 \pm 0.31	0.71 \pm 0.28	.32
C3a (ng/mL)	604 \pm 571	1331 \pm 619	.01 ^a
C3a/C3 \times 1000	0.96 \pm 0.79	3.23 \pm 4.24	<.001 ^b
TCC (U/mL)	36 \pm 34	53 \pm 28	.07
CRP (mg/L)	55 \pm 51	33 \pm 24	.41
TxB ₂ (pg/mL)	194 \pm 92	237 \pm 155	.19
Elastase (ng/mL)	539 \pm 337	1006 \pm 287	.03 ^a
Neop/creat (μ mol/mol)	837 \pm 488	906 \pm 476	.71

C, complement component; TCC, terminal complement complex; CRP, C-reactive protein; TxB₂, thromboxane B₂; neop/creat, neopterin/creatinine ratio.

^ap < .05; ^bp < .01, by Wilcoxon two-sample test.

concentrations were significantly different between survivors and nonsurvivors. The differences for the C3a/C3 ratios were mainly caused by significantly increased concentrations of C3a in the nonsurvivors. Terminal complement complex showed a tendency toward higher concentrations in nonsurvivors compared with survivors (p = .07).

Because five patients died before day 5, 51 patients were left for classification into subgroups with or without multiple organ failure. Of these 51 patients, multiple organ failure was diagnosed in 18 cases. Figure 1 shows the mean \pm SEM values of six mediators during the 2-wk study period in patients with and without multiple organ failure. On day 1, terminal complement complex, thromboxane B₂, and C3a concentrations were significantly higher in patients with multiple organ failure, while C-reactive protein concentration was lower on days 1 and 2. The most protracted differences between patients with and without multiple organ failure were found for elastase. Concentrations of elastase were significantly higher in patients with multiple organ failure for practically the whole first week after injury. Neopterin/creatinine

ratios did not show any significant difference between both groups during the first week. However, significantly higher neopterin/creatinine ratios were found in patients with multiple organ failure on day 8 (p = .04) and on day 10 (p = .005), while there was an indication of significance on day 12 (p = .06).

DISCUSSION

In the present report, we prospectively evaluated inflammatory mediators in relation to subsequent multiple organ failure and mortality. We studied a homogeneous group of severely traumatized patients, who had at least two severe or one severe plus two major lesions in different body regions (Injury Severity Score of \geq 33). This finding contrasts with the results of most other reports (7, 9, 12, 33), which evaluated a much wider range of "multiple"-injured patients, including those patients with an Injury Severity Score of <18 points. In the present study, a smaller range of Injury Severity Scores was evaluated; hence, the differences between groups in the present study will become less easily evident. On the other hand, if differences between groups occur, they could be pathophysiologically more relevant.

Complement and neutrophil activation, expressed by C3a or C3a/C3 ratios and elastase concentrations, respectively, appeared to be the most significant mediators for differentiation between survivors and nonsurvivors. This finding is in agreement not only with the results of other trauma patient studies, but also with results from studies involving patients undergoing major elective surgery and patients with sepsis (8, 10–12, 20, 21, 34, 35).

The most important finding of our study is that there were significantly higher circulating concentrations of complement activation (C3a and terminal complement complex), as well as thromboxane B₂ concentrations, on the first postinjury day in patients with subsequent multiple organ failure compared with those patients without subsequent multiple organ failure. Moreover, elastase concentrations were significantly increased practically the entire first week in the patients with subsequent multiple organ failure.

In contrast, C-reactive protein concentrations were initially higher in patients without multiple organ failure. This finding is not in agreement with a previous report (6), which showed a similar increase in C-reactive protein concentrations in both patient groups with and without multiple organ failure during the first 4 days after injury, with a significant increase in C-reactive protein concentrations in multiple organ failure patients from day 5 onward. We also could not demonstrate a positive correlation between severity of

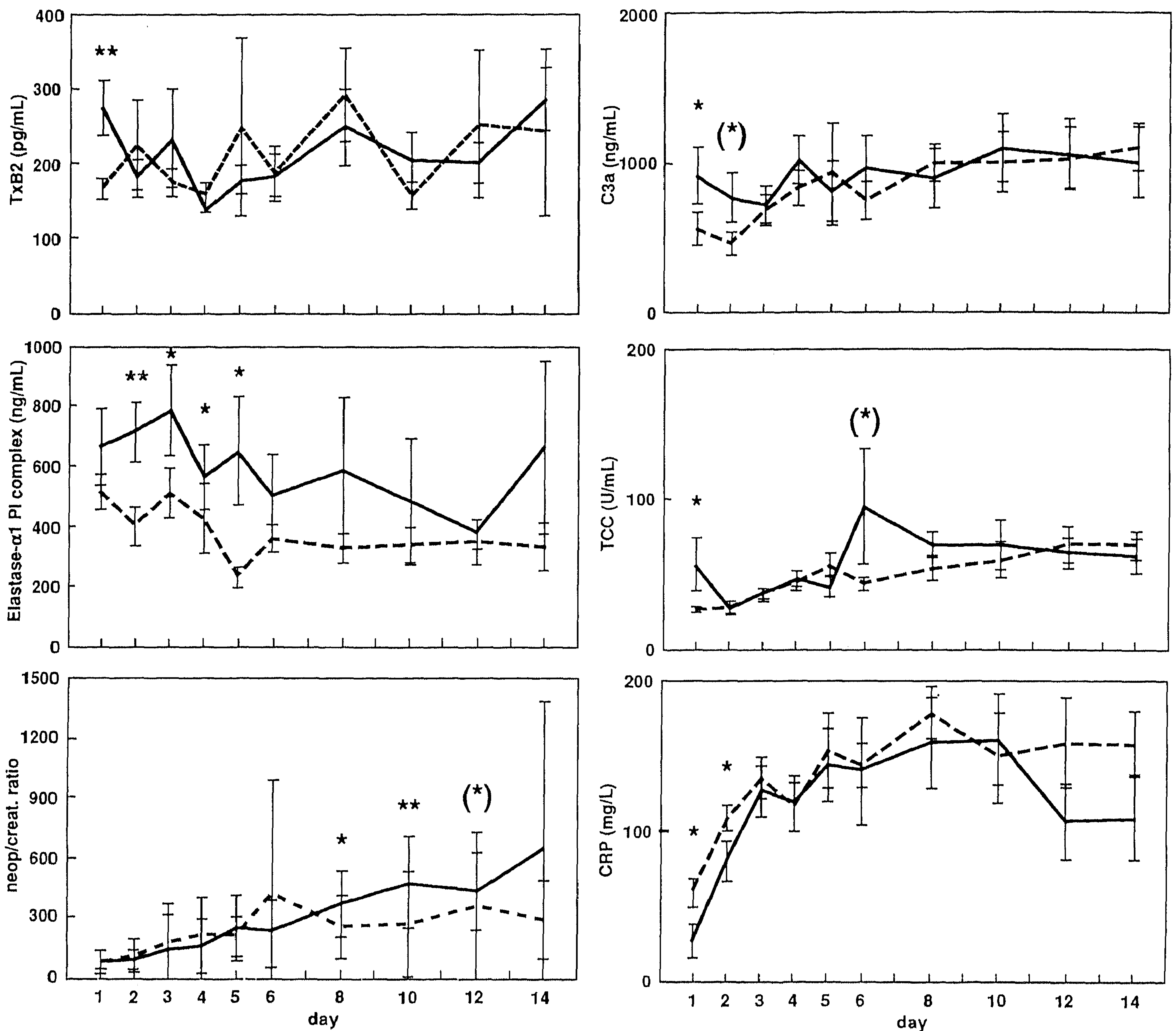


Figure 1. Mean \pm SEM values of C3a, terminal complement complex (TCC), C-reactive protein (CRP), thromboxane B₂ (TxB₂), elastase, and neopterin/creatinine (neop/creat) during a 2-wk intensive care unit observation period in 51 multiple trauma patients with multiple organ failure (solid line, n = 18) and without multiple organ failure (broken line, n = 33). The p values are indicated by asterisks: * $p < .10$; * $p < .05$; and ** $p < .01$, by the Wilcoxon test.

injury, as expressed by Injury Severity Score (data not shown), and C-reactive protein response, while other reports (15–17) showed that the magnitude of (surgical) trauma correlated well with the concentrations of C-reactive protein production. A possible explanation could be that the patients in the present study all had such severe trauma that this situation led to similar C-reactive protein concentrations according to the “all or nothing phenomenon” theory of Colley et al (36). On the other hand, it remains questionable to what extent liver damage and hepatic insufficiency may

contribute to the initial lower C-reactive protein production in patients developing multiple organ failure.

The role of the prostanoid thromboxane B₂ in the development of ARDS and multiple organ failure remains unclear. Some authors (19, 37) reported a positive correlation with subsequent ARDS, while others (38) could not confirm this finding. We could only demonstrate a significantly higher concentration of thromboxane B₂ on the first posttraumatic day in patients with subsequent multiple organ failure.

Neopterin concentrations in blood and urine have been shown to predict the outcome of patients with viral infections (including acquired immunodeficiency syndrome), autoimmune diseases, and graft vs. host reactions (39). Also, increased concentrations of neopterin are associated with poor outcome in multiple trauma and sepsis patients (6, 7, 39). Since neopterin is exclusively eliminated by the kidneys in a creatinine-like manner (23, 24), plasma neopterin concentrations should be used in reference to creatinine. Nast-Kolb et al. (6) concluded in their study on 69 multiple trauma patients that neopterin was a reliable parameter in predicting subsequent organ failure from days 2 to 5, but after this period, increased neopterin concentrations were mainly caused by retention due to renal insufficiency (6). In the present series, we therefore used the corrected neopterin concentrations during the entire observation period. We could only demonstrate a significant increase of the neopterin/creatinine ratio in multiple organ failure patients in the second week. This finding is in agreement with the finding of Nathan (40), who concluded that it apparently takes several days for macrophages after activation to fully develop their inflammatory capacity.

The present data support the view that complement activation plays a central and early role in the inflammatory cascade, leading to complications and poor outcome in multiple trauma patients. Complement activation is fundamental for bacterial opsonization and recruitment of inflammatory cells by chemoattraction. Complement activation elicits the release of lysosomal enzymes, such as elastase, and oxygen radicals by means of neutrophils, thus contributing to the defense against microorganisms, but also leading to cell and tissue damage that ultimately may result in organ failure (11, 34). Elastase appears to be not only a marker of severity of injury and a mediator leading to proteolysis of a great variety of normal tissue substances, but also a factor significantly correlating with final outcome.

The present study underlines the importance of the complement system and neutrophil activity in the early posttraumatic phase, not only in terms of mortality, but also in terms of the major complicating syndrome, multiple organ failure. Prevention of a continuous activation of the complement system and ongoing triggering of neutrophils (e.g., by adequate treatment of hypovolemic shock and optimal reoxygenation, thorough excision of necrotic tissue, prevention of compartment syndrome, etc.) are key goals in the early management of multiple trauma patients. Finally, these data support the hypothesis that multiple organ failure is the result of an excessive,

uncontrolled, autodestructive activation of inflammatory cells and mediators (2).

ACKNOWLEDGMENTS

We thank C. Wilfing for the administration of this study, I. Jung, A. Schiesser, and M. Pold for data processing, and all clinical staff of the participating trauma centers, who made this study possible.

REFERENCES

1. Trunkey DD: Trauma. Accidental and intentional injuries account for more years of life lost in the US than cancer and heart disease. *Sci Am* 1983; 249: 20-27
2. Goris RJA, te Boekhorst TPA, Nuytinck JK, et al: Multiple organ failure: Generalized autodestructive inflammation? *Arch Surg* 1985; 120:1109-1115
3. Deitch EA: Multiple organ failure. Pathophysiology and potential future therapy. *Ann Surg* 1992; 216:117-134
4. Baue AE (Ed): Multiple Organ Failure: Patient Care and Prevention. St Louis, Mosby-Year Book, 1990
5. Nerlich ML: Quantification of organ failure. In: Shock, Sepsis and Organ Failure. Schlag G, Redl H, Siegel J (Eds). First Wiggers-Bernard-Conference. Berlin, Heidelberg, New York, Springer-Verlag, 1990, pp 66-82
6. Nast-Kolb D, Waydhas C, Jochum M, et al: Biochemische Faktoren als objektive Parameter zur Prognoseabschätzung beim Polytrauma. *Unfallchirurg* 1992; 95:59-66
7. Waydhas C, Nast-Kolb D, Jochum M, et al: Inflammatory mediators, infection, sepsis, and multiple organ failure after severe trauma. *Arch Surg* 1992; 127:460-467
8. Zilow G, Sturm JA, Rother U, et al: Complement activation and the prognostic value of C3a in patients at risk of adult respiratory distress syndrome. *Clin Exp Immunol* 1990; 79:151-157
9. Nuytinck JKS, Goris RJA, Redl H, et al: Posttraumatic complications and inflammatory mediators. *Arch Surg* 1986; 121:886-890
10. Hack CE, Nuijens JH, Felt-Bersma RJF, et al: Elevated plasma levels of the anaphylatoxins C3a and C4a are associated with a fatal outcome in sepsis. *Am J Med* 1989; 86:20-26
11. Heideman M, Hugli TE: Anaphylatoxin generation in multi-system organ failure. *J Trauma* 1984; 24:1038-1043
12. Fosse E, Mollnes TE, Aasen AO, et al: Complement activation following multiple injuries. *Acta Chir Scand* 1987; 153:325-330
13. Pepys MB: C-reactive protein fifty years on. *Lancet* 1981; i:653-657
14. Heinrich PC, Castell JV, Andus T: Review article: Interleukin-6 and the acute phase response. *Biochem J* 1990; 265:621-636
15. Stahl W, Singh A, Marcus M: Responses of opsonic substances to major trauma and sepsis. *Crit Care Med* 1985; 13:779-782
16. Roumen RMH, van Meurs PA, Kuypers HHC, et al: Serum interleukin-6 and C-reactive protein responses in patients after laparoscopic or conventional cholecystectomy. *Eur J Surg* 1992; 158:541-544
17. Dominioni L, Dionigi R, Cividini F: Determinations of C-reactive protein and alpha-1-antitrypsin for quantitative assessment of surgical trauma. *Eur J Surg Res* 1980; 33(Suppl 1)
18. Dictionary of Prostaglandins and Related Compounds. Schrör K, Smith EF (Eds). München, Medikon Verlag, 1990
19. Slotman GJ, Burchard KW, Gann DS: Thromboxane and prostacyclin in clinical acute respiratory failure. *J Surg Res* 1985; 39:1-7
20. Tanaka H, Sugimoto H, Yoshioka T, et al: Role of granulocyte elastase in tissue injury in patients with septic shock

- complicated by multiple-organ failure. *Ann Surg* 1991; 213:81-85
21. Duswald KH, Jochum M, Schramm W, et al: Released granulocytic elastase: An indicator of pathobiochemical alterations in septicemia after abdominal surgery. *Surgery* 1985; 98:892-899
 22. Fuchs D, Hausen A, Reibnegger G, et al: Neopterin as a marker for activated cell-mediated immunity: Application in HIV infection. *Immunol Today* 1988; 9:150-155
 23. Huber C, Troppmair J, Rokos H, et al: Neopterin heute. *Dtsch Med Wochenschr* 1987; 112:107-113
 24. Werner ER, Bichler A, Dakenbichler G, et al: Determinations of neopterin in serum and urine. *Clin Chem* 1987; 33:62-66
 25. Roumen RMH, Redl H, Schlag G, et al: Scoring systems and blood lactate in relation to the development of ARDS and multiple organ failure in severely traumatized patients. *J Trauma* 1993; 35:349-355
 26. Baker SP, O'Neill B, Haddon W, et al: The injury severity score: A method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974; 14:187-196
 27. American College of Surgeons: Hospital trauma index. *Bull Am Coll Surg* 1980; 64:28-32
 28. Zilow G, Naser W, Rutz R, et al: Quantitation of the anaphylatoxin C3a in the presence of C3 by a novel sandwich ELISA using monoclonal antibody to a C3a neoepitope. *J Immunol Methods* 1989; 121:261-268
 29. Deppisch R, Schmitt V, Bommer J, et al: Fluid phase generation of terminal complement complex as a novel index of bioincompatibility. *Kidney Int* 1990; 37:696-706
 30. Flynn JT, Henry JM, Perkowski SZ: Phospholipase A₂ stimulated release of prostaglandins from the isolated, perfused rabbit liver. *Can J Physiol Pharmacol* 1981; 59:1268-1273
 31. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818-829
 32. Roumen RM, Schers TJ, de Boer HH, et al: Scoring systems for predicting outcome in acute hemorrhagic necrotizing pancreatitis. *Eur J Surg* 1992; 158:167-171
 33. Kapur MM, Jain P, Gidh M: The effect of trauma on serum C3 activation and its correlation with Injury Severity Score in man. *J Trauma* 1986; 26:464-466
 34. Gardinali M, Padalino P, Vesconi S, et al: Complement activation and polymorphonuclear neutrophil leukocyte elastase in sepsis. Correlation with severity of disease. *Arch Surg* 1992; 127:1219-1224
 35. Pacher R, Redl H, Frass M, et al: Relationship between neopterin and granulocyte elastase plasma levels and the severity of multiple organ failure. *Crit Care Med* 1989; 17:221-226
 36. Colley CM, Fleck A, Goode AW, et al: Early time course of the acute phase protein response in man. *J Clin Pathol* 1983; 36:203-207
 37. Deby-Dupont G, Braun M, Lamy M, et al: Thromboxane and prostacyclin release in adult respiratory distress syndrome. *Intensive Care Med* 1987; 13:167-174
 38. Oettinger W, Mayo K, Stager MA, et al: Thromboxane-A₂ und Granulozyten-Elastase nach schwerem Trauma—Beziehungen zu Verlaufskomplikationen und Überlebensraten. *Wien Klin Wochenschr* 1989; 23:805-813
 39. Strohmaier W, Redl H, Schlag G, et al: D-erythro-neopterin plasma levels in intensive care patients with and without septic complications. *Crit Care Med* 1987; 15:757-760
 40. Nathan CF: Secretory products of macrophages. *J Clin Invest* 1987; 79:319-326

ETHICS

Information on the following subjects of Ethics is available from the Society of Critical Care Medicine:

- Consensus Report on the Ethics of Foregoing Life-Sustaining Treatment in the Critically Ill
- Attitudes of Critical Care Medicine Professionals Concerning Forgoing Life-Sustaining Treatments
- Attitudes of Critical Care Medicine Professionals Concerning Distribution of Intensive Care Resources

Contact: Society of Critical Care Medicine
8101 East Kaiser Boulevard, Suite 300
Anaheim, CA 92808-2259

Phone: (714) 282-6000; Fax: (714) 282-6050