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Volume 127, Number 1

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Inflammatory Mediators, Infection, Sepsis, and Multiple Organ Failure After Severe Trauma

Christian Waydhas, MD; Dieter Nast-Kolb, MD; Marianne Jochum, PhD; Arnold Trupka; Susann Lenk; Hans Fritz, PhD; Karl-Heimo Duswald, MD; Leonhard Schweiberer, MD

• The relation of (multiple) organ failure (OF) to the release of inflammatory mediators and the incidence of infection and sepsis was studied prospectively in 100 patients with multiple trauma (injury severity score = 37). Sixteen patients died of OF, 47 patients survived OF, and 37 patients had no OF. Fifteen (24%) of the patients with OF showed no signs of infection. In patients with early onset of OF ($n = 45$), infection followed with a lag of 2 or more days. In 16 (44%) of these patients, infection led to a deterioration in organ function. With late onset of OF ($n = 18$), infection preceded OF in nine patients. Polymorphonuclear leukocyte-elastase, neopterin, C-reactive protein, lactate, antithrombin III, and phospholipase A discriminated significantly among the three outcome groups. Of all factors, only polymorphonuclear leukocyte-elastase showed a difference between patients with and without infection or sepsis, respectively. These data indicate that infection might not play a crucial role in the pathogenesis of posttraumatic OF in a substantial portion of patients with trauma. Early OF, especially, seems to be mainly influenced by the direct sequelae of tissue damage and shock (eg, the release of inflammatory mediators). Since infection and sepsis did not lead to an augmented release of mediators in patients with trauma, the role of both entities remains unclear.

(*Arch Surg.* 1992;127:460-467)

The major cause of late death after severe blunt trauma is (multiple) organ failure (OF). It is usually attributed to infectious complications that develop in the posttraumatic course leading to dysfunction of the respiratory and other organ systems.¹⁻⁴ Sepsis is the commonly used denominator for the clinical presentation of the syndrome. Thus, sepsis is generally regarded as the main cause of OF and late death after severe trauma. As a rule, a proven bacterial focus is mandatory in most definitions of sepsis. However, in the initial descriptions of multiple

OF,^{5,6} it was already pointed out that despite the uniformity of the syndrome, a variety of causes other than infection may lead to organ dysfunction. For example, a clinical picture resembling sepsis can be found in acute pancreatitis in humans. Experimental studies were able to induce a sepsislike syndrome with nonbacterial, nonendotoxic inflammatory stimuli.^{7,8} Thus, several authors suggested that multiple OF after trauma may be the direct consequence of mediators released during tissue damage and circulatory shock and not of infectious sequelae.^{9,10} To describe this syndrome, terms such as "whole body inflammation"¹¹ or "nonbacteremic clinical sepsis"¹² were introduced. To further elucidate the role of inflammatory mediators and infection in the development of multiple OF, we have performed a prospective study in severely injured patients.

PATIENTS AND METHODS

During the study period (1986 to 1990), traumatized patients arriving at our emergency department were examined immediately by a member of the study team and included in the prospective study if all of the following criteria were met: (1) less than 6 hours between accident and admission to the emergency department; (2) between 16 and 70 years of age; and (3) severe injuries of at least two body regions (head/brain, thorax, abdomen, skeletal system) or three major fractures. Severe injuries included the following: (1) head—unconsciousness for more than 60 minutes or with dilated pupil(s), cerebrospinal fluid rhinorrhea or otorrhea, unstable facial bone fracture; (2) thorax—more than three fractured ribs, sternum fracture, pneumothorax/hemothorax, lung contusion, aortic rupture, cardiac tamponade, rupture of the diaphragm; (3) abdomen—hollow or parenchymal organ laceration, renal contusion or laceration; (4) skeletal system—vertebral lesion (fracture of vertebral body or arch, ligamentous injury with dislocation, spinal cord injury), pelvic fractures, fractures of the femur, tibia, and/or humerus, amputations proximal to the toes or digits.

Collection of blood samples for routine and biochemical laboratory testing as well as recording of clinical data, including diagnostic and therapeutic interventions, drug and infusion therapy, Glasgow Coma Scale, and cardiopulmonary monitoring data, were started within 30 minutes after arrival of the patient in the emergency department and continued on a 6-hour basis. After 48 hours, the interval was extended to 24 hours for a period of 14 days. After 2 weeks, the clinical course was recorded until either transfer to a general ward or death.

Biochemical measurements using commercially available test kits included polymorphonuclear leukocyte (PMN)-elastase (E.

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From the Departments of Surgery (Drs Waydhas, Nast-Kolb, Duswald, and Schweiberer, Mr Trupka, and Ms Lenk) and Clinical Chemistry and Clinical Biochemistry (Drs Jochum and Fritz), Klinikum Innenstadt, Ludwig Maximilians-University, Munich, Germany.

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Merck, Darmstadt, Germany), C-reactive protein (Behringwerke, Marburg, Germany), antithrombin III (Kabi, Stockholm, Sweden), neopterin (Henning, Berlin, Germany), and phospholipase A (Boehringer, Mannheim, Germany). Testing for bacteria from the urinary tract and the bronchial system was routinely done twice a week or when clinically indicated. Blood cultures were taken when the body temperature rose above 38.5°C. Swabs for bacterial cultures were taken from all catheter tips and from wounds when indicated. The following definitions were used. Sepsis was assumed when two signs of the following signs 1 to 3 in addition to sign 4 occurred: (1) temperature of 38.5°C or greater; (2) white blood cell count (WBC) greater than or equal to $15 \times 10^9/L$ or less than or equal to $5 \times 10^9/L$; (3) thrombocytes less than or equal to $100 \times 10^9/L$ or a fall of greater than or equal to 30% in 24 hours; and (4) culture-proved bacterial focus.

Pneumonia was supposed when one sign of the following signs 1 to 2 plus one sign of signs 3 to 4 occurred: (1) temperature of 38.5°C or greater; (2) WBC of $12 \times 10^9/L$ or greater; (3) positive bacterial culture; (4) abnormal roentgenographic signs typical of pneumonia. Urinary tract infections were considered to cause the following signs: (1) positive culture with more than 10^4 bacteria per milliliter; (2) temperature of 38.5°C or greater; (3) WBC of $12 \times 10^9/L$ or greater. Catheter infection was considered to cause the following signs: (1) temperature of 38.5°C or greater; (2) WBC of $12 \times 10^9/L$ or greater; (3) positive culture from catheter tip. Respiratory failure was indicated by the following signs: need of mechanical ventilation and PO_2 /fraction of inspired oxygen of 280 mm Hg or less or positive end-expiratory pressure of 8 mm Hg or greater for at least 24 hours. Renal failure was indicated by a creatinine concentration of $177 \mu\text{mol}/L$ or greater for at least 48 hours. Liver failure was indicated by a bilirubin level of $51 \mu\text{mol}/L$ or greater for at least 48 hours. Disseminated intravascular coagulation was indicated by the following signs: (1) thrombocyte level of $100 \times 10^9/L$ or less or a fall of 30% or more in 24 hours; (2) partial thromboplastin time of 50 seconds or more for 24 hours; (3) reptilase time of 22 seconds or more for 24 hours (similar to the test for thrombin time, but with use of the heparin-independent thrombinlike enzyme reptilase instead of thrombin).¹³ Gastrointestinal tract failure was indicated by endoscopically proved ulceration with bleeding or acalculous cholecystitis.

Multiple OF was assumed if two or more organ systems failed at the same time. Statistical testing was done with the nonparametric Wilcoxon Test for two samples and the χ^2 test with Yates' correction. Differences were considered significant with P values less than .05 and highly significant with P values less than .01. The study was carried out in accordance with the Ethical Committee of the Ludwig Maximilians-University, Munich, Germany.

RESULTS

One hundred seventeen patients entered the study. Seventeen patients died during the first 24 hours; the remaining 100 primary survivors formed the basis of the following results. The mean injury severity score was 37 points (range, 13 to 66 points). There were 74 male and 26 female patients with a mean age of 38 years. Sixteen patients (16%) died between days 3 and 28 (median surviving time, 16 days).

The overall incidence of OF, infection, and bacterial sepsis is listed in Table 1. The bacterial foci of sepsis were pneumonia ($n=18$), wound infection ($n=5$), urinary tract infection ($n=2$), catheter infection ($n=1$), and peritonitis ($n=1$). In Table 2, patients are divided into nonsurvivors (group 1), survivors with OF (group 2), and survivors without OF (group 3). The incidence of pneumonia and bacterial sepsis did not differ significantly between groups 1 and 2 ($P>.1$). The rate of pneumonia, infection, and bacterial sepsis was significantly higher in groups 1

Table 1.—Incidence of Organ Failure, Infection, and Sepsis in 100 Patients With Trauma*

Factor	%
Organ failure	63
Isolated	31
Multiple	32
Pneumonia	46
Urinary tract infection	8
Wound infection	15
Catheter infection	1
Peritonitis	1
No infection	43
Sepsis	27

*The occurrence of more than one infectious focus in a patient is possible.

Table 2.—Incidence of Multiple Organ Failure (OF), Infection, and Bacterial Sepsis in Three Outcome Groups of Patients With Trauma*

	Group 1	Group 2	Group 3
No. of patients	16	47	37
Mean ISS	43	39	32
Multiple OF, No. (%)	15 (94)	16 (34)	...
Infection, No. (%)	13 (81)	35 (74)	9 (24)
No infection, No. (%)	3 (19)	12 (26)	28 (76)
Sepsis, No. (%)	8 (50)	17 (36)	2 (5)

*Group 1 comprises nonsurvivors; group 2, survivors with OF; and group 3, survivors without OF. Percent sign indicates percentages within each group. ISS indicates injury severity score.

and 2 compared with group 3 ($P<.0001$). However, nearly a quarter of the patients in groups 1 and 2 did not show signs of bacterial infection at any time. Ninety-three percent of all cases of bacterial sepsis were observed in patients with OF, whereas only 7% of all patients with bacterial sepsis had no organ insufficiency. Although a high coincidence of bacterial sepsis and OF could be verified, several patients with infection and even sepsis had no development of OF.

In Fig 1, the starting points of OF, infections, and sepsis in relation to trauma are displayed. In most cases ($n=45$), OF became obvious during the first 2 days after trauma (usually respiratory failure). A second peak emerged between days 6 and 8, predominantly due to liver failure. This second rise either represents the onset of late OF or a deterioration in the patient's condition with the development of multiple OF. Infections came up at day 3 and remained fairly constant for about a week. Bacterial sepsis occurred with a slight delay. The leading infection was pneumonia. There was a high correlation of pneumonia with the duration of mechanical ventilation. While patients who were being mechanically ventilated for less than 5 days had an 8% rate of intrapulmonary infection, the incidence of pneumonia rose to 71% as the duration of ventilation increased. Patients from groups 1, 2, and 3 were ventilated 15.8, 12.5, and 4.7 days, respectively.

According to the onset of OF, two groups were formed (early and late onset of OF) and the starting point of infection and sepsis relative to OF was defined in each single patient. The condensed data are shown in Table 3. Of

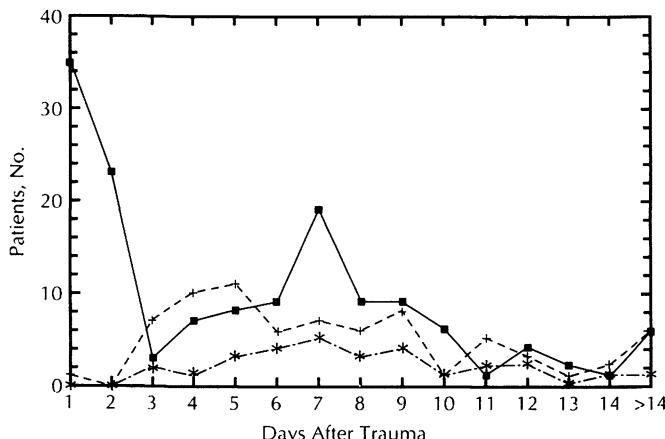


Fig 1.—Frequency distribution of onset of organ failures, infection, and sepsis in 100 patients with trauma during 14 posttraumatic days. The number on the y-axis signifies the number of patients in whom organ failure (squares), infection (plus signs), and sepsis (asterisks) starts on the specific day.

Table 3.—Onset of Infection in Relation to Onset of Organ Failure (OF) in Patients With Trauma With OF Starting Within the First 3 Days After Trauma (n=45)

	Infection	Sepsis
Onset of infection/sepsis		
≥2 d before OF
1 d before to 1 d after OF	1	1
≥2 d after OF	35	18
No infection/sepsis	9	26

45 patients with early onset of OF (within the first 3 days after trauma), 36 showed signs of infection. Of those, bacterial complications and sepsis could be recognized only 2 or more days after OF in 35 (97%) and 34 (95%) patients, respectively. In 16 patients (44%), infection was followed by a deterioration of organ function. Twelve of 18 patients with late OF (after the third posttraumatic day) suffered from bacterial complications (Table 4). Infection preceded or coincided with the onset of OF in nine patients (75%), whereas three patients (25%) showed signs of infection only several days after late OF.

The release of mediators and indicators of inflammatory reactions in the three outcome groups is displayed in Fig 2. Polymorphonuclear leukocyte-elastase showed a highly significant difference ($P < .01$) between groups 1 or 2 vs 3 throughout the whole observation period and between groups 1 vs 2 ($P < .05$) after the third day. Neopterin was significantly ($P < 0.05$) higher in group 1 (nonsurvivors) compared with survivors (group 2 or 3) from the second day onward and between groups 2 vs 3 after the fourth posttraumatic day. The production of C-reactive protein was significantly different ($P < .01$) between all outcome groups starting on the third day after trauma. A significantly higher accumulation of lactate ($P < .01$) could be observed in nonsurvivors (group 1) compared with survivors with OF (group 2) throughout the 14 days of observation. Moreover, lactate levels of group 2 differed significantly ($P < .01$) from those of group 3 during the first 8 days. Antithrombin III showed a significantly lower inhibitory activity ($P < .01$) in groups 1 or 2 vs 3 all the time and between groups 1 and 2 (nonsurvivors vs survivors with OF) ($P < .05$) after the first week. In contrast, a significant difference in plasma levels of phospholipase A

Table 4.—Onset of Infection in Relation to Onset of Organ Failure (OF) in Patients With Trauma With OF Starting After the Third Posttraumatic Day (n=18)

	Infection	Sepsis
Onset of infection/sepsis		
≥2 d before OF	4	1
1 d before to 1 d after OF	5	4
≥2 d after OF	3	1
No infection/sepsis	6	12

among the three groups became obvious only after more than a week following trauma.

For the same factors, a comparison was accomplished between patients suffering from infection/sepsis and those who did not sustain these entities. To exclude the above-described influence of outcome, the comparison was performed separately within each outcome group. In the following figures, the results of the largest group (survivors with OF, group 2) are shown, which are similar to the results of the other two groups.

Figure 3 represents the graphs for patients with and without infection. No significant differences were observed for any of the factors, except for PMN-elastase, which differentiated between infected and noninfected patients.

The plasma levels of mediators of patients with and without sepsis are shown in Fig 4. The elastase values were significantly higher in patients in whom these signs of bacterial sepsis developed than in those in whom signs did not develop. This difference became obvious from the second posttraumatic day onward with P values usually varying between .01 and .05. None of the other factors (neopterin, C-reactive protein, lactate, antithrombin III, phospholipase A) showed a clear discrimination between patients with and without bacterial sepsis at any time.

COMMENT

In 1980, Fry et al¹ published results of 553 patients who underwent emergency operations, of whom 38 had development of multiple OF. Thirty-four of these patients showed signs of infection and the authors concluded that infection and its systemic manifestations were the most crucial factor in the evolution of OF in patients after surgery. Infection was found in 46 of 47 patients with lethal adult respiratory distress syndrome in a necropsy study.¹⁴ Thus, a major role of infection in the pathogenesis of OF was established for patients following surgery and for patients with internal disease.

In the original communications of multiple OF,^{5,6} however, it has been shown that in addition to infection, other inflammatory processes or hypotension may lead to multiple OF. In our prospective series of multiply injured patients, about a quarter of all individuals with isolated or multiple OF did not show any signs of bacterial infection at all. Similar observations were made by several other authors: Goris et al⁷ failed to prove infection in 24 (43.6%) of 55 severely injured patients with lethal multiple OF. Border¹⁰ found negative blood cultures in two thirds and no septic focus in one third of his patients with multiple OF following trauma. In another study 49 (56%) of 88 patients with adult respiratory distress syndrome did not show signs of infection.¹⁵ Moreover, in a further investigation, no sepsis was observed in six (23%) of 26 patients with multiple OF.¹⁶ However, in this study, the cases of

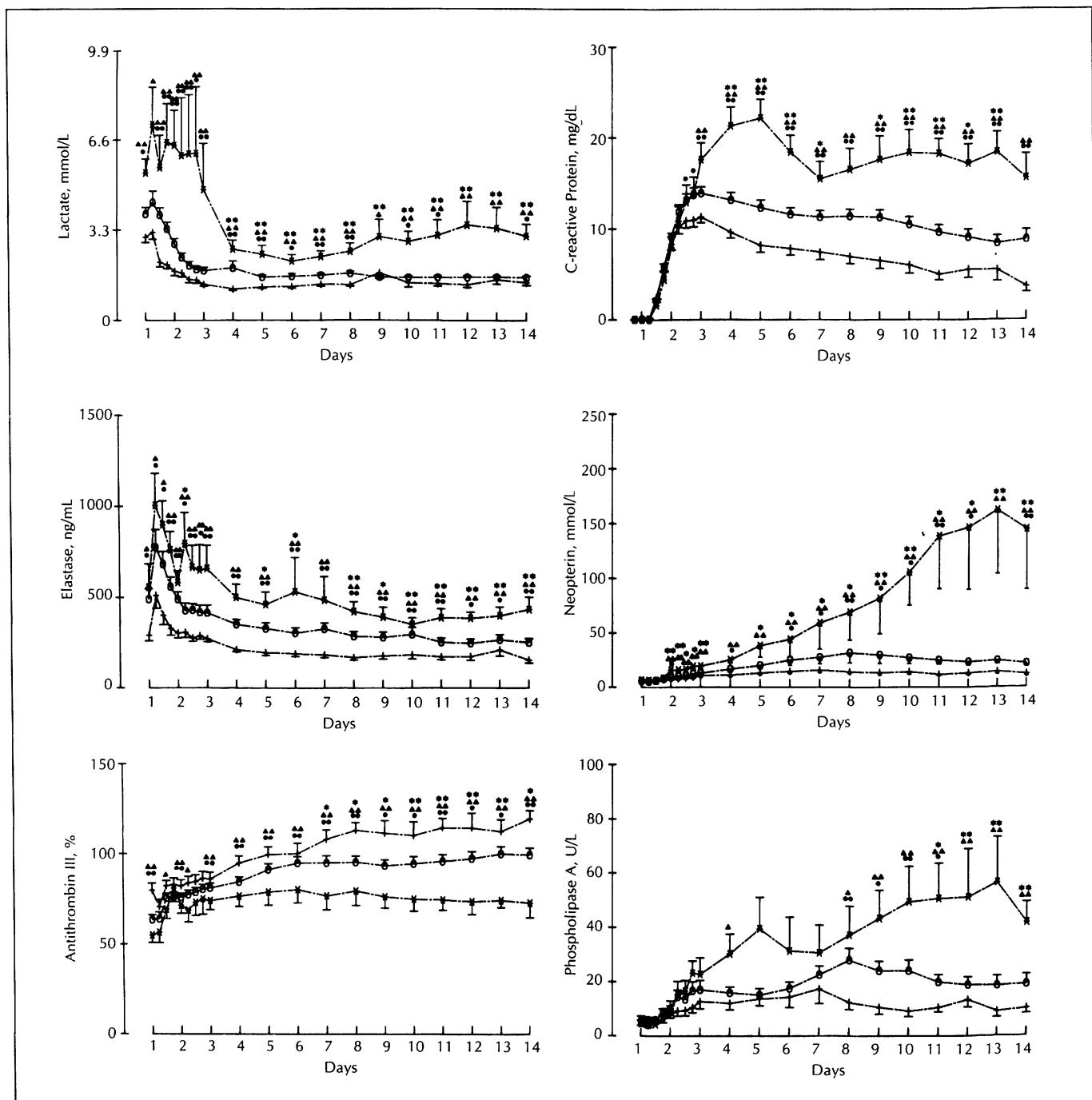


Fig 2.—Mean (±SEM) values of lactate, polymorphonuclear leukocyte–elastase, antithrombin III, C-reactive protein, neopterin, and phospholipase A in the following three outcome groups: group 1—16 nonsurvivors (asterisks-connected dashed line); group 2—47 survivors with organ failure (open circles-connected dashed line); and group 3—37 survivors without organ failure (plus signs-connected dashed line). Asterisk indicates $P < .05$; double asterisks, $P < .01$ group 1 vs group 2; closed circles, $P < .05$; double closed circles, $P < .01$ group 1 vs group 3; triangles, $P < .05$; and double triangles, $P < .01$ group 2 vs group 3.

13 patients with sepsis but without multiple OF were reported. This result corresponds to that obtained with our nine patients suffering from sepsis/infection without organ dysfunction (Table 2). Therefore, it can be concluded that sepsis does not necessarily lead to OF.

All these communications provide reasonable evidence that multiple OF following trauma is present in 25% to 50% of patients without signs of bacterial infection. Thus, OF occurs without the pathogenetic pacemaker of infection in a substantial portion of patients with trauma. To

further evaluate the role of infection in patients with OF, we analyzed the temporal relation between onset of OF and diagnosis of infection.

In those patients who sustained early OF within 3 days after trauma, a substantial part showed no signs of infection (20%) or sepsis (58%) in our study. Those who suffered from infectious entities usually did so only 2 or more days after the manifestation of OF. Similar observations were made by other authors¹⁷ who could not prove sepsis in 15 severely injured patients with early multiple OF. In

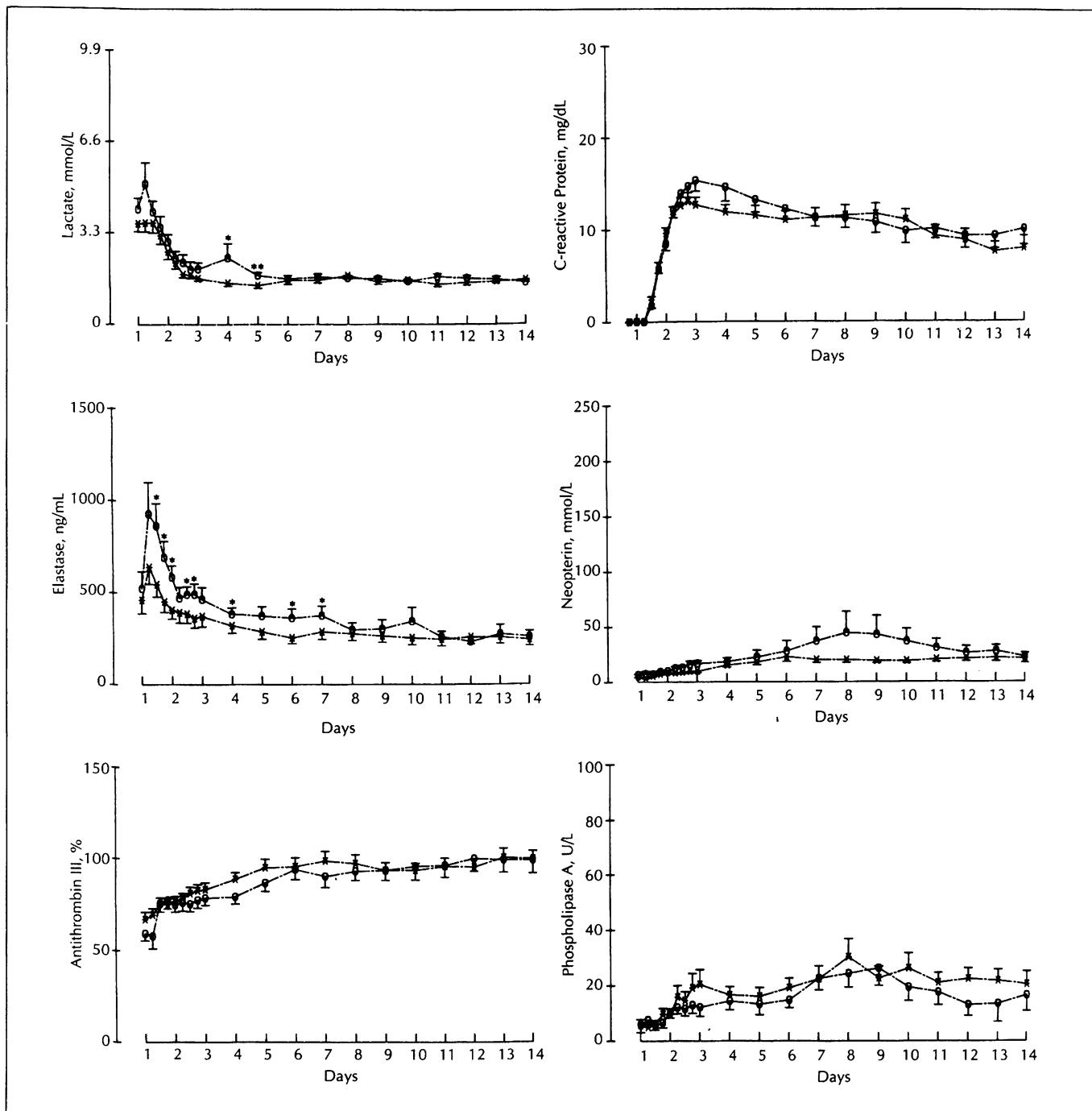


Fig 3.—Mean (±SEM) values of lactate, polymorphonuclear leukocyte–elastase, antithrombin III, C-reactive protein, neopterin, and phospholipase A in survivors with organ failure (n=47) with infection (n=35) (asterisks-connected dashed line) and without infection (n=12) (open circles-connected dashed line). Asterisk indicates $P < .05$; double asterisk, $P < .01$ infection vs no infection.

patients with early OF, the severity of the initial trauma and its biochemical sequelae seemed responsible for the development of OF. Infection and sepsis followed, if at all, with a lag of at least 2 days. Infections did not influence the posttraumatic course in 56% of the patients in our series. On the other hand, in 44% a further deterioration in the patient's organ dysfunctions became obvious when infections supervened.

Eighteen patients had development of late OF after the third posttraumatic day. In this group of patients, infection could not be observed in 33%. If present, however, signs of infection were recorded at the same time or even

before OF started in 75% of patients. Therefore, a causative role of bacterial infection in the development of OF can be assumed in this subset of patients. This observation corresponds to those of other authors¹⁷ who have found sepsis in all patients with delayed onset of OF. Monitoring of mediators and indicators of the inflammatory response to a variety of stimuli allows a more precise description of the body's reaction than can be achieved with clinical data alone. The release of these factors may be triggered by direct tissue trauma, tissue hypoxia in circulatory shock, infection, and sepsis or others. Some of them (eg, C-reactive protein, neopterin, lactate) are indi-

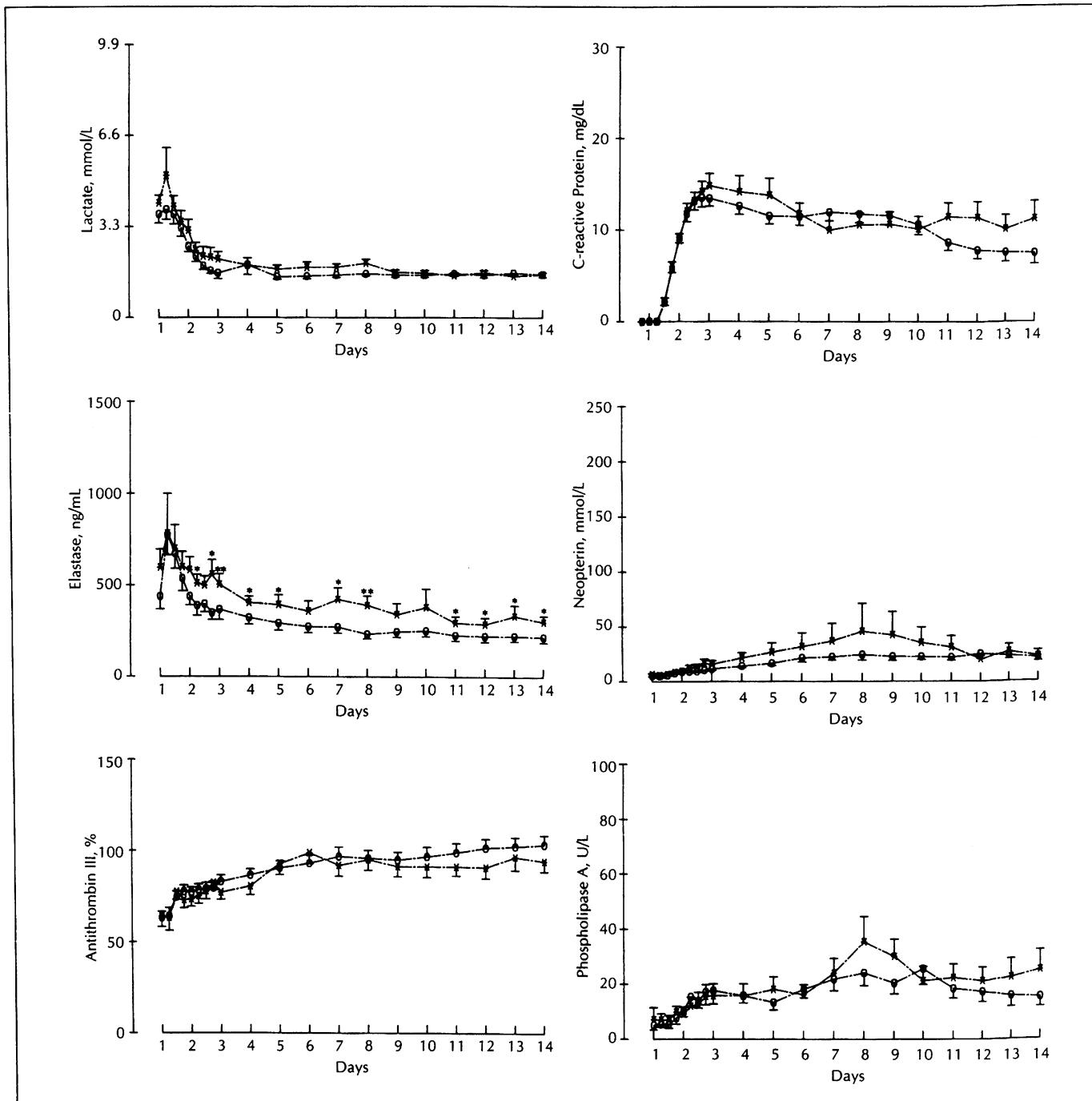


Fig 4.— Mean (\pm SEM) values of lactate, polymorphonuclear leukocyte-elastase, antithrombin III, C-reactive protein, neopterin, and phospholipase A in survivors with organ failure ($n=47$) with sepsis ($n=17$) (asterisks-connected dashed line) and without sepsis ($n=30$) (open circles-connected dashed line). Asterisk indicates $P<.05$; double asterisk, $P<.01$ sepsis vs no sepsis.

cators of the inflammatory response and do not seem to have any causative role of their own in the development of OF. Others, such as PMN-elastase, antithrombin III, or phospholipase A may lead to proteolytic tissue damage,¹⁸ play a role in the formation of thromboembolism,¹⁹ or enhance the arachidonic acid pathway.²⁰ In experimental models and clinical studies,^{7,8} a pathogenetic significance could be attributed to these mediators; their actual role in the development of posttraumatic OF, however, remains incompletely defined. Many other biochemical pathways not determined in this study are involved in the process of OF. Yet, those factors presented herein are known to

correlate highly with traumatic or septic events. For example, the neutral proteinase PMN-elastase is released from the primary inflammatory cells (PMN granulocytes) by major surgery^{18,21} and trauma^{11,22-24} and correlates well with the severity of trauma.^{11,22} Furthermore, elastase allowed the differentiation between surgical patients without complications, septic survivors, and septic nonsurvivors in one series¹⁸ and the septic nonsurvivors and nonseptic patients in another.²⁵ Neopterin, an indicator of macrophage activity, showed significant differences between survivors and nonsurvivors²⁶ and septic and non-septic patients in an intensive care unit.²⁵ C-reactive pro-

tein is an acute-phase reactant that may serve as an indicator of the activation of cytokine pathways. It is not only raised in septic shock^{18,27} but also shows an elevation in patients who have sustained trauma with significant differences between mild injuries, severe injuries without complications, and those with sepsis.²⁸ Antithrombin III, the main inhibitor of the coagulation system, has been shown to differ significantly between survivors and nonsurvivors suffering from septic shock,^{27,19} septic and non-septic patients,¹⁹ and patients with trauma with and without hypotension.²⁹ Phospholipase A, an inducer of the arachidonic acid metabolism, was shown to correlate highly with hypotension in septic shock.²⁰

In our series of 100 severely injured patients, all of these mediators and indicators of the inflammatory response showed a high correlation with the patients' outcome. The differentiation among nonsurvivors (all with OF), survivors with OF, and survivors without OF was possible already within the first hours after the accident using the plasma levels of elastase, lactate, and antithrombin III or after a few days with the help of neopterin, C-reactive protein, and phospholipase A values. These differences were observed before infections or bacterial sepsis could be anticipated and remained throughout a period of 2 weeks. We therefore conclude that it is mainly the severity of the initial trauma and its biochemical sequelae that trigger the release of inflammatory mediators and indicators not only in the immediate posttraumatic period but also in the later course where it can lead to a prolonged disturbance of the homeostasis.

Since blunt trauma as well as bacterial complications and sepsis initiate the release of mediators and indicators (see above), we compared the reaction of these mediators in severely traumatized patients with and without infection and sepsis. Increased levels of inflammatory reactants should be expected in individuals with infectious complications. Surprisingly, only the elastase values were significantly higher in patients with sepsis and infections as compared with the other patients, whereas no other mediator seemed to be affected by sepsis or infection. Although it cannot be ruled out completely that sepsis starts in different patients at different times, thus smoothing differences, Fig 1 shows a peak of septic events between days 5 and 9. One might assume that due to the permanent influx of intact bone marrow-derived cells, the activation of PMN granulocytes precedes this period (Fig 4), thus indicating a contribution of PMN cell constituents to the development of sepsis. In contrast, the body's ability to produce or consume (eg, antithrombin III) the other mediators in an augmented amount seems to be either exhausted after the trauma-induced activation or does not even take place. Therefore, these mediators do not seem to play a crucial role for onset or duration of the septic event in the later course. The observation of a high rate of infections in patients with trauma, despite a lack of mediator release, might lead to the speculation that one main stem of our diagnosis of infection, namely the bacterial focus, may be just a sign of bacterial overgrowth due to the failing immune system and not represent a genuine infection leading to OF in several patients.

In conclusion, isolated and multiple OF in severely injured patients seems to have a variety of causes and cannot be attributed exclusively to infection. (1) In about a quarter of patients with OF, infection does not seem to play a significant role at any time. (2) Of those patients with infection, three quarters show an early onset of OF

long before infection starts. In only half of them, infection or sepsis leads to a consecutive deterioration of organ functions. In patients with late onset of OF, infection and sepsis precede the disturbance of organ function and seem to have pathogenetic significance. (3) The release or activation of mediators and indicators of the inflammatory response are mainly dependent on the severity of injuries. Only PMN-elastase showed a correlation with sepsis and infection, whereas the other factors were not influenced by bacterial complications, indicating that PMN cell constituents may contribute to the occurrence of sepsis.

The cause of OF is not always clear in the individual patient with trauma. The classic bacterial infection is not the sole contributor to the multiple OF syndrome. Since the term *sepsis* is closely related to a bacterial infection, we suggest that this diagnosis no longer be used in patients who have sustained trauma.

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