Original Articles

Disturbances of Selected Plasma Proteins in Hyperdynamic Septic Shock

J. Witte¹, M. Jochum¹, R. Scherer², W. Schramm¹, K. Hochstrasser⁴ and H. Fritz²

¹Departments of Surgery and ²ENT-Diseases, Klinikum Großhadern, ³Department of Internal Medicine and ⁴Institute of Clinical Chemistry and Clinical Biochemistry, University of Munich, and ²Department of Experimental Medicine, Max-Planck-Institute for Biochemistry, Martinsried, Federal Republic of Germany

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Abstract. This study was performed on patients (n = 18) suffering from strictly defined hyperdynamic septic shock. Plasma factors (C-reactive protein, acid a1-glycoprotein, fibrinogen, fibrinopeptide A, fibrinogen-fibrin split products, factor XIII, antithrombin III, complement factors C3 and C4, inter-α-trypsin-inhibitor and α2-macroglobulin) measured during hyperdynamic septic shock were highly abnormal. The activation and consumption of clotting, fibrinolytic and complement factors due to systemic specific proteinases (such as thrombokinase or plasminogen activators) seemed to be intensified by the nonspecific proteolytic activity of granulocytic proteinases probably released by the action of endotoxins. Possible therapeutic measures to maintain the endogeneous defence mechanism against enhanced proteolysis during septic shock are discussed.

Key words: Septic shock – Coagulation – Fibrinolytic and complement systems – Granulocytic proteinases – Nonspecific proteolysis – Proteinase inhibitors

Introduction

Bacterial sepsis and its most serious complication, septic shock play an essential role in the pathogenesis of acquired coagulation disorders which may lead to disseminated intravascular coagulation [10, 11, 13, 18a, 20]. The endotoxins (phospholipid-polysaccharide-peptide complexes) released from the cellular walls of gram negative bacteria primarily cause endothelial lesions [8], which secondarily activate the clotting, fibrinolytic and complement systems.

It is also known from a number of studies that in the course of serious inflammatory processes, a massive degranulation of leukocytes occurs caused directly by endotoxin and inflammatory mediators released from other cells. Consequently, lysosomal enzymes are liberated which normally degrade phagocytosed material within the cells. By their release from the cells, however, they intensify the inflammatory process in at least two different ways. Proteinases such as thrombokinase and plasminogen activators activate the clotting, fibrinolytic and complement systems by inducing proenzyme-enzyme conversion due to specific proteolytic cleavages. These reactions are responsible for the well-known specific consumption of the blood proteins leading to disseminated intravascular coagulation (DIC). The severe consumption of plasma proteins also seems to be caused, to a large degree, by non-specific degradation by leukocytic proteinases such as elastase and cathepsin G liberated by endotoxin [14, 23]; acute leukemia and the Gram-negative sepsis are clinically relevant examples [14]. The possibly life-threatening coagulation disturbances observed during these disorders are caused mainly by released granulocytic enzymes. To obtain further information about the degree of involvement of specific activation or nonspecific proteolytic degradation in the consumption of plasma factors during septic shock, we followed the plasma levels of selected factors. A clinical trial was carried out in patients suffering from clearly defined hyperdynamic septic shock.

Materials and Methods

Patients

Eighteen patients (13 males, 5 females) with septic shock were examined. In 13 patients, the septic foci
were localized in the abdomen, two patients had abscesses in the urogenital region. Isolated pneumonia was responsible for the sepsis in two other patients. In one case (patient 14) extra-abdominal primary disease was found (Table 1). Since very different clinical courses are described as hyperdynamic septic shock [4, 10], the patients in this study had to show the following:

1. **Septic Criteria**
   - raised temperatures with a minimum of at least 38.5°C
   - two positive blood cultures and/or positive cultures in other related samples
   - leukocytosis with more than 15000 cells/mm³ or leukopenia with less than 5000 cells/mm³
   - thrombocytopenia with less than 130000 cells/mm³
   - all the clinical signs of septic shock.

2. **Hemodynamic Criteria**
   - cardiac index above 6 (l/min/m² body surface)
   - total peripheral vascular resistance (TPR) below 600 dyn x s x cm⁻⁵
   - mean arterial blood pressure within the normal range (mmHg).

Patients satisfying all these conditions were observed for 4 days. All hemodynamic and biochemical parameters were noted after 6, 12, 18, 24, 36, 48, 72 and 96 h ($\bar{x}_6 - \bar{x}_{96}$) after taking the initial values ($\bar{x}_0$).

**Therapy**

The following measures were performed: Surgical intervention for the septic focus, volume substitution with human albumin regulated according to the pulmonary capillary wedge pressure, continuous low dose heparin therapy (200–400 U/h), infusion of 100–400 µg/min dopamine (to maintain urine output of at least 80–100 ml/h), administration of 30 mg/kg body weight of methylprednisolone every 6 h up to 48 h, medication with antibiotics according to the sensitivity patterns of the microorganisms, and parenteral nutrition as well as mechanical ventilatory assistance.

**Bacteriological Examinations**

Bacteria were detected in blood cultures, tracheal secretions, drainages and microscopic preparations of wounds. All results were confirmed by at least one finding identical to the original. Blood cultures (aerobic and anaerobic) were taken at the beginning of the episode of fever or during rigors and were incubated immediately.

**Hemodynamic Parameters**

The catheters (CVP, $p_{pa}$) were inserted under aseptic conditions and were left in for the period of treatment. A 3-lumen thermostor-balloon-catheter (7-F-Swan-Ganz-Thermodilution catheter), placed in the pulmonary artery from the subclavian vein, was used to measure cardiac output with a cardiac output computer (no. 9510, Edward's Laboratories). Injections of 10 ml 0.9% NaCl (0° – 5°C) were made at the same phase of the respiratory cycle. The results of the cardiac output are the average values of three measurements each done immediately one after the other (range 5%–10%). The circulatory variables calculated from these data (cardiac index, TPR) were ascertained using standard formulae.

**Hematological Measurements**

Leukocytes were counted using a Coulter-Counter Model B. Thrombocyte counts were performed using the Neubauer's counting chamber.

The mean values of lactate in blood were increased ($3.4 \pm 0.5$ mmol/l, $p < 0.005$) at the beginning of the observation period. The values for patients who died during the shock phase increased after 96 h up to 12.8 ± 3.3 mmol/l. On the other hand, the levels of lactate decreased ($2.4 \pm 0.3$ mmol/l) after 96 h in patients who survived the shock phase.

**Estimation of Plasma Factors**

Plasma samples were prepared from specimens of citrated blood. If the samples were not analyzed immediately they were stored at −30°C.
Statistics

Unless otherwise indicated, results obtained from the blood specimens of our patients were compared with normal values (x̄) stated in the literature.

Statistical evaluation was performed by the Student-T-Test. p values ≤ 0.05 were considered to be significant.

Results

The present examinations were carried out in a prospective manner with 18 patients satisfying all the criteria of hyperdynamic septic shock. Within the observation period of 96 h, four patients died and the remainder survived the shock event. However, all these patients except one succumbed within 6 and 84 days after the end of the observation period either due to the direct sequelae of shock (respiratory insufficiency, oliguria or anuria) or to toxic heart failure and underlying malignant disease.

Bacteriology

The bacteriological results of blood and other cultures are shown in table 1. Gram-negative bacteria predominate. Despite performing daily blood cultures, no organisms were detected in the blood specimens of six patients, probably because of prior treatment with antibiotics. These six subjects, however, contained organisms in the other samples examined.

Table 1. Bacteriological results in hyperdynamic septic shock (n = 18)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Blood culture</th>
<th>Trachea</th>
<th>Drainage</th>
<th>Wound specimen</th>
<th>Urin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Klebsiella, Streptococcus</td>
<td>Klebsiella</td>
<td>negative</td>
<td>negative</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Pyocaeaneus, E. coli</td>
<td>E. coli</td>
<td>negative</td>
<td>Staphylococcus, E. coli, Pyocaeaneus</td>
<td>E. coli</td>
</tr>
<tr>
<td>3</td>
<td>Pyocaeaneus, Enterobacter</td>
<td>Klebsiella, Pyocaeaneus</td>
<td>Pyocaeaneus</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>4</td>
<td>Klebsiella</td>
<td>Klebsiella</td>
<td>negative</td>
<td>E. coli, Enterococcus</td>
<td>E. coli</td>
</tr>
<tr>
<td>5</td>
<td>Klebsiella</td>
<td>negative</td>
<td>E. coli</td>
<td>negative</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>6</td>
<td>negative</td>
<td>E. coli</td>
<td>Staphylococcus</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>7</td>
<td>Enterococcus, Streptococcus, E. coli</td>
<td>Streptococcus, E. coli</td>
<td>negative</td>
<td>negative</td>
<td>E. coli (?)</td>
</tr>
<tr>
<td>8</td>
<td>Serratia, Klebsiella</td>
<td>Serratia, Klebsiella</td>
<td>negative</td>
<td>E. coli, Streptococcus, Klebsiella</td>
<td>negative</td>
</tr>
<tr>
<td>9</td>
<td>Streptococcus</td>
<td>Streptococcus, Klebsiella</td>
<td>negative</td>
<td>Staphylococcus</td>
<td>negative</td>
</tr>
<tr>
<td>10</td>
<td>E. coli</td>
<td>negative</td>
<td>E. coli</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>11</td>
<td>negative</td>
<td>Klebsiella</td>
<td>Klebsiella, E. coli</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>12</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>14</td>
<td>Clostridium, Pyocaeaneus</td>
<td>negative</td>
<td>Clostridium, Pyocaeaneus</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>15</td>
<td>negative</td>
<td>Klebsiella, E. coli, Pyocaeaneus</td>
<td>Klebsiella, E. coli, Pyocaeaneus</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>16</td>
<td>E. coli, Enterococcus</td>
<td>E. coli</td>
<td>E. coli</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>17</td>
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<td>E. coli</td>
<td>E. coli</td>
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<td>E. coli</td>
</tr>
<tr>
<td>18</td>
<td>negative</td>
<td>E. coli</td>
<td>E. coli</td>
<td>Enterococcus, E. coli</td>
<td>negative</td>
</tr>
</tbody>
</table>

Bacteria were detected in blood cultures, tracheal secretions, drainages and wound specimens. All results were confirmed by two identical findings.
The initial value was twice as high as the standard
of the patients who died during the investigation phase decreased to well below the normal value.

The total peripheral vascular resistance (TPR) (545.8 ± 41.4 dyn x s x cm⁻²) was significantly
in the whole group (Table 2), characteristic of hyperdynamic shock. With therapy, especially volume replacement, TPR tended towards normal values of 868.5 ± 78.4 dyn x s x cm⁻² after 96 h. The four patients who died during the observation period showed a more rapid approach of TPR to standard values. This was, however, related to a falling cardiac index.

Hematological Data

Fifteen of the 18 patients (Table 2) had a marked leukocytosis with an average of 21366 ± 2526 cells/mm³ at the beginning of the observation period. This value decreased slightly until the 96th h (17254 ± 1728 cells/mm³).

Three of the 18 patients (10, 11, and 15) had a constant leukopenia with 4633 ± 1073 cells/mm³ at the beginning and 3633 ± 555 cells/mm³ after 96 h.

The numbers of thrombocytes were low, with an average of 129139 ± 17441 cells/mm³ (x₀: 200000 to 300000 cells/mm³). The values decreased until the 24th h to 80757 ± 13396 cells/mm³ and remained at that level to the end of the observation period (Table 2).

Acute-Phase Proteins

The so-called acute-phase proteins are synthesized in the liver at higher rates during severe inflammatory processes. As the shock event may significantly impair liver function [22, 29], a reduction of the efficiency of protein synthesis by the liver had to be excluded. This was achieved by measuring the plasma levels of the acute-phase proteins fibrinogen, C-reactive protein, and acid α₁-glycoprotein. The levels of these three were significantly increased during the observation period.

Fibrinogen: At the beginning of the trial, the average fibrinogen level reached the upper limit of the normal range (x₀ = 359.7 ± 23.4 mg/dl; xₙ = 180–380 mg/dl). During the observation period, the values decreased to x₉₀ = 293.5 ± 17.4 mg/dl, but this difference was not significant (p > 0.05). As fibrinogen is probably consumed due to the activation of the clotting cascade, the true plasma levels might be clearly higher than the given values.

C-reactive protein [28] is considered to be a nonspecific protein accompanying primary and secondary inflammatory processes. Its plasma level increases prior to those of other acute-phase proteins. Therefore, determination of C-reactive protein is of special interest in achieving an early diagnosis. The plasma levels of C-reactive protein were significantly increased due to the massive inflammatory process during the observation period (x₀ = 13.5 ± 1.3 mg/dl; xₙ = 10.4 ± 1.6 mg/dl; xₙ = <1.2 mg/dl).
Acid α₁-glycoprotein, another protein accompanying inflammatory reactions, serves mainly for the diagnosis of liver diseases. The meaning of its increase, however, is not yet clear [28]. In this study, the plasma levels of the acid α₁-glycoprotein were significantly above the normal range of the observation period ($\bar{x}_0 = 90\text{ mg/dl} \pm 100\%$; $\bar{x}_0 = 139.3 \pm 7.9\%$ or $\bar{x}_96 = 123.9 \pm 15.2\%$).

Factors of the Clotting and Fibrinolytic Systems

Even at the beginning of the observation period the values of fibrinopeptide A (Fig. 1) were four times higher than the standard values ($\bar{x}_0 = 13.1 \pm 2.7\text{ ng/ml}$; $\bar{x}_n = < 3.0\text{ ng/ml}$). They remained at that level during the 4-day investigation phase ($\bar{x}_{96} = 18.1 \pm 4.5\text{ ng/ml}$).

The plasma levels of the fibrinogen-fibrin split products (Fig. 1) just increased above the standard range ($\bar{x}_0 = 21.4 \pm 4.1\text{ μg/ml}$; $\bar{x}_n = 5 - 10\text{ μg/ml}$) and returned to normal in the course of 96 h ($\bar{x}_{96} = 10.7 \pm 1.7\text{ μg/ml}$).

Factor XIII (Fig. 2) was significantly reduced from the onset ($\bar{x}_0 = 46.1 \pm 4.9\%$ of the standard value). It increased only slightly during the observation period ($\bar{x}_{96} = 52.9 \pm 4.8\%$ of the standard value).

The plasma concentration of antithrombin III (Fig. 2) showed a highly significant reduction at the beginning of the observation period ($\bar{x}_0 = 47.4 \pm 2.8\%$ of the standard value). The antithrombin III level of the surviving patients increased slowly over the course of 96 h ($\bar{x} = 58.9 \pm 5.6\%$ of the standard value). The value of the four patients who died during the septic shock phase, however, decreased terminally below the starting values ($\bar{x}_{96} = 32.0 \pm 4.0\%$ of the standard value).

Complement Factors

A significantly low plasma concentration of C3 ($\bar{x}_0 = 70.1 \pm 4.3\%$ of the normal value) was found at the start of the septic shock phase (Fig. 3) and showed no tendency to return to normal during the following 4 days ($\bar{x}_{96} = 65.3 \pm 6.7\%$ of the normal value). In contrast, the plasma level of C4 was not significantly reduced during the whole observation period. Values of $\bar{x}_0 = 82.2 \pm 11.2\%$ and $\bar{x}_{96} = 74.5 \pm 11.2\%$ of the normal values are still within the normal range of this factor (Fig. 3).

Inter-α-Trypsin-Inhibitor (ITI) and α₂-Macroglobulin (α₂M)

As a screening investigation, ITI was examined in the blood samples of only ten patients (1–10). A constant significant reduction ($p \leq 0.001$) of native, acid-labile ITI was observed ($\bar{x}_0 = 42.7 \pm 3.6\text{ mIU/ml}$; $\bar{x}_{96} = 46.4 \pm 3.4\text{ mIU/ml}$; $\bar{x}_n = 50 - 80\text{ mIU/ml}$) during the whole observation period (Fig. 4). In contrast, the concentration of the acid-stable ITI-derived inhibitor was constantly and significantly ($p \leq 0.01$) increased ($\bar{x}_0 = 15.7 \pm 1.7\text{ mIU/ml}$; $\bar{x}_{96} = 21.7 \pm 2.5\text{ mIU/ml}$; $\bar{x}_n = 6 - 9\text{ mIU/ml}$).
The average plasma level of α₂-macroglobulin (α₂M) was significantly (p ≤ 0.005) diminished in all patients at the beginning of the trial ($\bar{x}_0 = 48.8 \pm 5.2\%$, Fig. 4) and showed no tendency to normalization ($\bar{x}_{96} = 46.8 \pm 4.5\%$ of the standard value).

Discussion

In spite of numerous reports of sepsis or septic shock, the pathogenesis of these diseases remains largely unknown. Since a clear definition of “septic shock” is not generally accepted, it is not surprising that etiology, hemodynamic criteria, severity or outcome are not comparable within or among the various studies. We have focused our efforts, therefore, on carrying out the biochemical measurements in patients with a definite diagnosis of hyperdynamic septic shock according to Messmer [25]. Although the hyperdynamic phase is commonly considered to be the initial stage of the disorder, the present results demonstrate that the plasma levels of the measured variables were already abnormal when the first clinical and haemodynamic signs appeared.

Leukocytes, particularly the granulocytes, may play a central part in the changes described. Aasen et al. [1] showed in an experimental study on lethal canine endotoxin shock that there was a definite correlation between the initial fall in leukocyte count (probably combined with degranulation of these cells) and the appearance of the leukocytic enzyme, elastase, in plasma. After a short delay, the well-known disturbances of clotting, fibrinolysis and complement systems arose indicating that consumption of the plasma proteins might be due, at least in part, to the activity of liberated leukocytic proteasines [18a]. The prominent leukocytosis following the initial leukopenia is thought to be one of the early defence reactions against the endotoxin. It is, therefore, apparent that the criterion of a “leukocytosis of more than 15 000 cells/mm$^3$” is an important but certainly not an early mark of sepsis [3, 10, 15]. On the other hand, it is agreed that leukopenia in the later phase of the disease carries a very bad prognosis usually indicating a fatal outcome [10]. Because of the small number ($n = 3$) of patients with leukopenia in our study, this assumption could not be verified statistically.

As an essential though indirect indication for the considerable liberation of proteasines from various body cells, especially leukocytes, during septic shock, we assumed a substantial consumption or turnover of plasma proteasine inhibitors throughout the observation period. Studies clearly demonstrated that the turnover of the inter-α-trypsin-inhibitor (ITI) is signi-
studies in vitro showed that, of various proteinases examined, granulocytic elastase in particular was able to split off the acid-stable inhibitor (ITI_{180000}) from the native ITI (ITI_{160000}) most rapidly [16]. Since in the present study the level of native ITI was significantly reduced whereas the concentration of the acid-stable ITI-derived inhibitor was considerably elevated, it may be deduced that granulocytic proteinases are responsible for the prominent turnover of ITI in septic shock and septicemia. Measurement of the ITI turnover could be an indirect marker of leukocytic proteinase activity although the biological function of ITI_{180000} or ITI_{30000} is not yet clear. The broad-spectrum proteinase inhibitor a2-macroglobulin (a2M) seems to be mainly responsible for inhibition and elimination of neutral and acidic proteinases liberated from various body cells thus leading to a severe consumption of this most important proteinase-elimination resource [5, 16, 27, 34]. Since a dramatic change, exceeding variations within the standard range, has not been noted during most inflammatory processes, the remarkably low level of a2M throughout the septic shock phase is especially striking. Obviously, considerable amounts of various proteinases were permanently released into the circulation and eliminated by a2M. In the light of this finding an important function can be ascribed to a2M in protecting the organism against nonspecific proteolysis during septic shock.

Consumption of antithrombin III, the most essential inhibitor for maintaining homeostasis of the clotting system [16], normally reflects the liberation of thrombin and factor Xa, whose inhibition and elimination is primarily effected by AT III. With heparin medication to prevent thrombosis or disseminated intravascular coagulation, the assumption of AT III is even further intensified, since the heparin AT III complex also reacts with other activated clotting enzymes or plasma kallikrein [5]. On the other hand, very recent results from our laboratory [18, 18a] have shown that purified AT III is proteolytically inactivated even by catalytic amounts of purified granulocytic elastase. Though in vitro effects should be transferred to in vivo conditions only with reservation, we assume that at least part of the AT III consumption measured in the present trial may be due to proteolysis by granulocytic proteinases, especially in the patients who died during the septic shock phase.

Besides turnover or consumption of several plasma proteinase inhibitors, the significantly low levels of two other plasma proteins, the fibrin-stabilizing clotting factor XIII and complement factor C3, may be also indicative of enhanced proteolytic activity due to degranulation of leukocytes. F XIII [24] seems to be preferred substrate of granulocytic proteinases, since in experimental septicemia the especially high consumption of this clotting factor could be prevented by previous systemic application of a specific inhibitor of granulocytic elastase and cathepsin G [30]. Moreover, Egbring et al. [7] demonstrated that in the course of septicemia in man the active transglutaminase (subunit A) and the carrier protein (subunit S) of F XIII were consumed to a comparable degree. The reduction of both subunits, however, is not consistent with the usual consumption of F XIII during blood clotting, since subunit A and F XIII activity disappear completely after coagulation of plasma, whereas subunits S remains unchanged. As the elastase-like granulocytic proteinase (ELP) caused a similar reduction of the activity of both F XIII subunits in plasma, it is very likely that proteolysis by ELP is involved in patients with septicemia or septic shock.

Activation of the complement cascade in endotoxemia [2, 26] proceeds primarily via the alternative pathway. This may also be deduced from the clearly lower level of complement factor C3 compared to C4 during the shock phase. In this respect, two facts are of special interest; first, endotoxins can trigger the release of elastase from granulocytes [1, 7] and second, elastase enables cleavage of complement factor C4 in such a way that direct activation of the alternative pathway occurs [2, 19]. It may be assumed, therefore, that liberated elastase could at least be partly responsible for the significant reduction of C3 throughout the hyperdynamic phase.

Although there are numerous indirect indications that nonspecific proteolytic degradation, particularly due to granulocytic enzymes, may be involved in the prominent consumption of proteinase inhibitors and other plasma proteins during the septic shock phase, it should be emphasized, that certainly a permanent activation of the clotting, fibrinolysis and complement cascades via system-specific proteinase occurred. An increased plasma concentration of fibrinopeptide A is especially remarkable in this respect. This first split product of fibrinogen during clotting is suggested to be highly characteristic for generated thrombin activity [23]. Similarly, activation of plasminogen and thus of fibrinolysis is responsible for the elevated plasma levels of fibrinogen split products [33].

Summarizing the results of our trial, it is clear that in hyperdynamic septic shock the natural defense mechanism against system-specific and nonspecific proteinases is considerably overstressed leading to severe consumption of many vital plasma proteins. Administration of suitable proteinase inhibitors [9] should primarily prevent the exhaustion of endo-
genous plasma inhibitors such as \( \alpha_2 \)M or AT III and thus help to maintain the physiological balance. However, until systemic administration of inhibitors of thrombin or granulocytic proteases is possible in humans, substitution with AT III [29] and \( \alpha_2 \)M concentrations might be a means of therapy.

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Priv.-Doz. Dr. J. Witte
Dept. of Surgery
University of Munich
Klinikum Großhadern
Marchioninstr. 15
D-8000 Munich 70
Federal Republic of Germany