Time Course of Hemostatic Abnormalities in Sepsis and its Relation to Outcome

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Objectives: To investigate the time course and the relation to prognosis of coagulation and fibrinolytic abnormalities in patients with septic shock.

Patients and Methods: Forty-eight consecutive patients admitted to the medical ICU with the diagnosis of septic shock (diagnosed by defined criteria) were studied. Mortality was 25 of 48. Mean age was 57 ± 7.3 years. Blood samples were obtained on days 1, 4, and 7 after hospital admission to measure tissue-type plasminogen activator antigen (t-PA), urokinase-type plasminogen activator (u-PA), plasminogen activator inhibitor antigen (PAI-1), plasminogen, α2-antiplasmin, fibrinogen, antithrombin III, protein C, protein S, thrombin-antithrombin complexes (TAT), D-dimer, and von Willebrand factor-related antigen (vWF:Ag).

Results: All patients showed marked abnormalities in both the coagulation and fibrinolytic systems. There were signs of coagulation activation and elevation of both activators and inhibitors of fibrinolysis. Nonsurvivors showed lower levels of protein C and antithrombin III and higher concentration of TAT than survivors. While both t-PA and PAI-1 concentrations were high in survivors and nonsurvivors, only survivors showed a progressive normalization of both parameters during the study period. Low plasminogen levels and plasminogen/α2-antiplasmin ratio were found in both groups, presenting a trend toward normalization only in survivors. The differences reported were not apparent at the time of hospital admission.

Conclusions: Septic shock is characterized by coagulation activation and fibrinolysis activation and inhibition. Nonsurvivors present a particular hemostatic profile characterized by a more marked activation of coagulation and a more intense inhibition of fibrinolysis. None of the abnormalities studied was significantly different between survivors and nonsurvivors at the time of hospital admission. In the presence of fibrin formation, nonsurvivors present a maintained imbalance in the fibrinolytic response determined by higher PAI-1 plasma concentration, probably contributing to their poor outcome. (Ches 1993; 103:1536-42)

ELISA = enzyme-linked immunosorbent assay; PAI-1 = plasminogen activator inhibitor 1; PG/AF = plasminogen/α2-antiplasmin ratio; TAT = thrombin-antithrombin complex; t-PA = tissue-type plasminogen activator; u-PA = urokinase-type plasminogen activator; vWF:Ag = von Willebrand factor-related antigen

Sepsis is characterized by a pathologic oxygen supply-dependent oxygen uptake and an abnormal tissue oxygen extraction. Possible causes of this phenomenon include a disturbed microcirculation and microembolization of peripheral tissues.1 Abnormalities of coagulation and fibrinolysis are frequently observed in patients with sepsis.2,3 Histologically, fibrin and microthrombi are commonly detected.4

Although components of Gram-positive bacteria can initiate the inflammatory cascade that characterizes sepsis, endotoxin from Gram-negative bacteria has been shown to play a major role in triggering the clinical and laboratory manifestations of sepsis.5,6 The vascular endothelium serves as a target organ for the action of endotoxin. The endothelial cell releases both activators and inhibitors of the fibrinolytic system. In vitro, endotoxin has been shown to change the properties of the vascular endothelium from profibrinolytic and anticoagulant to antifibrinolytic and procoagulant.7 It has been suggested that the regulation of the fibrinolytic system in sepsis may have a role in the subsequent development of disseminated intravascular coagulation, fibrin deposition, and microthrombi.7 Fibrin deposition and complement activation can cause extensive vessel wall damage and may be associated with multiple organ failure.8,9

Clinical studies have shown that sepsis is characterized by endothelial cell activation and a particular hemostatic profile, with biochemical evidence of activation of coagulation and sequential activation and inhibition of fibrinolysis.7,8 However, few studies have investigated the time course of those abnormalities in
septic patients and whether there is a difference in the severity of those abnormalities depending on the outcome.\textsuperscript{11-13}

To define the time course of the hemostatic abnormalities, we studied patients with septic shock over a one-week period. We hypothesized that nonsurvivors of septic shock could have an imbalance in the fibrinolytic response presenting a more strongly inhibited fibrinolysis that would favor the deposition of fibrin formed intravascularly during the coagulation process.

METHODS

Patients

With our Institutional Review Board approval, we studied 48 patients admitted to the medical ICU with the diagnosis of severe sepsis.\textsuperscript{14} At the time of hospital admission, all patients were in shock as defined by sepsis-induced hypotension, and the presence of signs of hypoperfusion, such as lactic acidosis, altered mental status, or oliguria.

Age (mean ± SEM) was 57 ± 7.3 years. Apache II score was 20.2 ± 2.9 in survivors and 23.3 ± 2.3 in nonsurvivors. Twenty-one (43 percent) had positive blood cultures (15 for Gram-negative bacilli, 6 for Gram-positive cocci, including 3 patients with both Gram-positive and Gram-negative microorganisms). Mortality was 25 of 48 (52 percent). Eight patients died before day 7. Six patients among survivors were discharged from the hospital before day 7. Twenty patients (42 percent) had adult respiratory distress syndrome (ARDS) according to the following criteria: Po2 <50 mm Hg with FiO2≥0.5; diffuse infiltrates on chest radiographs; no evidence of left ventricular failure (pulmonary capillary wedge pressure <18 mm Hg); and a compatible underlying clinical cause. Among patients with ARDS, mortality was 13 of 20 (65 percent).

Blood samples were taken at 8 AM starting the next morning the patient met the criteria for the diagnosis of septic shock, and then on days 4 and 7. The determination of thrombin-antithrombin complex (TAT) and urokinase-type plasminogen activator (u-PA) was done only on days 1 and 7. Blood was sampled from an indwelling

Table 1 — Hemostatic Parameters on Days 1, 4, and 7 in Patients With Septic Shock\textsuperscript{*}

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrinogen, mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Survivors</td>
<td>436 (t)</td>
<td>579 (t)</td>
<td>585.5 (†, §)</td>
<td>248 (160-333)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>590 (†)</td>
<td>651.5 (†)</td>
<td>816.5 (†)</td>
<td>96 (73-130)</td>
</tr>
<tr>
<td>Factor vWF:Ag(%)</td>
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<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>204.5 (†)</td>
<td>250 (†)</td>
<td>200 (†)</td>
<td>49 (92-453)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>266 (†)</td>
<td>266 (†)</td>
<td>225 (†)</td>
<td>41 (50-454)</td>
</tr>
<tr>
<td><strong>Antithrombin III (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Survivors</td>
<td>77 (†)</td>
<td>85.5 (50-150)</td>
<td>93.5 (‡)</td>
<td>49 (46-138)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>69 (t)</td>
<td>74 (†)</td>
<td>72 (†)</td>
<td>44 (106-146)</td>
</tr>
<tr>
<td><strong>Protein C (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>68 (†)</td>
<td>64.5 (†, §)</td>
<td>76.5 (†)</td>
<td>82.5 (60-160)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>57 (†)</td>
<td>49 (†)</td>
<td>52.5 (†, §)</td>
<td>31-99</td>
</tr>
<tr>
<td><strong>Protein S (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>78 (21-107)</td>
<td>81 (38-114)</td>
<td>83.5 (†)</td>
<td>85 (65-146)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>80 (30-130)</td>
<td>75 (51-129)</td>
<td>84 (†)</td>
<td>83 (45-150)</td>
</tr>
<tr>
<td><strong>TAT, ng/ml</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>9.3 (†)</td>
<td>6.1 (†, ‡)</td>
<td>13.4 (†, ‡)</td>
<td>1.0 (1.0-4.1)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>20.5 (†)</td>
<td>52.0 (†)</td>
<td>1.3 (†, ‡)</td>
<td>2.1 (1.5-9.0)</td>
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<tr>
<td><strong>DD-dimer, mg/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Survivors</td>
<td>3.95 (†)</td>
<td>3.43 (‡)</td>
<td>4.10 (†)</td>
<td>0.03 (0.03-5.22)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>3.89 (†)</td>
<td>3.40 (‡)</td>
<td>5.30 (†)</td>
<td>0.02 (0.00-11.37)</td>
</tr>
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<td><strong>Plasminogen (%)</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Survivors</td>
<td>75.9 (†)</td>
<td>103.5 (†, §)</td>
<td>90.6 (‡)</td>
<td>106.7 (47-265)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>62.2 (†)</td>
<td>66.4 (†)</td>
<td>76.5 (†)</td>
<td>43 (102-264)</td>
</tr>
<tr>
<td><strong>α&lt;sub&gt;-&lt;/sub&gt;antiplasmin (%)</strong></td>
<td></td>
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<tr>
<td>Survivors</td>
<td>108.5 (55-174)</td>
<td>111 (55-235)</td>
<td>105 (59-167)</td>
<td>92.5 (63.6-159)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>104 (33-188)</td>
<td>115 (51-258)</td>
<td>113.5 (65-243)</td>
<td></td>
</tr>
<tr>
<td><strong>Plasminogen/α&lt;sub&gt;-&lt;/sub&gt;antiplasmin ratio</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>0.68 (†)</td>
<td>0.81 (†)</td>
<td>0.83 (‡, §)</td>
<td>1.09 (0.56-1.76)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>0.64 (†)</td>
<td>0.58 (†)</td>
<td>0.64 (‡)</td>
<td>0.43 (1.03)</td>
</tr>
<tr>
<td><strong>PAI-1, ng/ml</strong></td>
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<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>47.5 (†)</td>
<td>33.2 (†, §)</td>
<td>38.5 (†, ‡)</td>
<td>15.2 (0.6-46.5)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>49.2 (†)</td>
<td>44.8 (†)</td>
<td>45.5 (†)</td>
<td>23 (131-231)</td>
</tr>
<tr>
<td><strong>t-PA, ng/ml</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>7.1 (†)</td>
<td>4.0 (†, ‡)</td>
<td>5.1 (†, §)</td>
<td>4 (0-12)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>6.0 (†)</td>
<td>8.2 (†)</td>
<td>7.2 (†)</td>
<td>2 (20-20)</td>
</tr>
<tr>
<td><strong>u-PA, ng/ml</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>2.05 (†)</td>
<td>2.10 (†)</td>
<td>2.45 (†, §)</td>
<td>1.1 (0.3-2.5)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>2.40 (†)</td>
<td>2.45 (†)</td>
<td>2.45 (†, §)</td>
<td>1.1 (0.3-2.5)</td>
</tr>
</tbody>
</table>

*Values are expressed as median and range.
†p<0.05 for the comparison with the control group.
‡p<0.05 for the comparison with day 1.
§p<0.05 for the comparison of survivors with nonsurvivors.
arterial catheter with minimal suction. The blood was centrifuged at 3,000 g for 15 min and the plasma was divided in aliquots and snap frozen at -40°C until used. Thirty healthy volunteers served as the control group. Samples from healthy volunteers were obtained through venipuncture. Although it is possible that indwelling catheter sampling could cause slight hemostatic abnormalities in patients, we think that the marked abnormalities found cannot be explained solely on these bases.

All patients were receiving prophylactic low molecular weight heparin subcutaneously. Volume expansion was performed by human serum albumin or synthetic starch and no patient received fresh frozen plasma.

Methods

Tissue-type plasminogen activator (t-PA) was measured by an enzyme-linked immunosorbent assay (ELISA) with the exception that all 96-well polyvinyl plates were precoated with goat IgG t-PA antibodies (Calbiochem, La Jolla, Calif) and stored during the study at -40°C. This measurement is sensitive to both free and complexed t-PA. Plasminogen activator inhibitor 1 (PAI-1) was measured with a murine monoclonal antibody based ELISA (Biopool AB, Umea, Sweden). The u-PA was measured by an ELISA method using monoclonal antibodies (Technoclone, GmBH, kindly donated by Immuno A.G., Vienna, Austria). Fibrin degradation products assay was performed using monoclonal antibodies to D-dimer fibrin fragments in an ELISA assay (Boehringer Mannheim). Protein C, protein S, α2-antiplasmin, plasminogen, and von Willebrand factor-related antigen (vWF:Ag) were measured by a Laurell rocket immunoelectrophoresis technique using rabbit antihuman antibodies (Boeringerwerke A.G., Marburg, Germany). Antithrombin III was measured by a chromogenic assay. The TATs were measured by an ELISA method (Boeringerwerke A.G., Marburg, Germany). Fibrinogen was measured by thrombin time assay.

The Wilcoxon and the Mann-Whitney tests with the Bonferroni correction were used to compare within-groups and between groups medians. Data are expressed as median and range.

Results

Results are summarized in Table 1. Patients with Gram-positive bacterial infections showed hemostatic abnormalities as severe as those with Gram-negative infections. Fibrinogen plasma levels were high in both groups on days 1, 4, and 7. Levels in nonsurvivors on day 7 were significantly higher than in survivors. The vWF:Ag levels were elevated during the study period in both groups, with no particular trend. No significant differences were found between survivors and nonsurvivors or between patients with and without ARDS on any particular day. However, pooling together all the determinations, regardless of the study day, there was a statistically significant difference in vWF:Ag between patients with ARDS (median, 250 percent; range, 68 to 912; n = 56) and those without ARDS (median, 212 percent; range, 20 to 690; n = 72).

Antithrombin III levels were significantly low only on day 1 in survivors and on days 1, 4, and 7 in nonsurvivors (Fig 1, upper panel). Survivors showed a trend toward normalization. On day 7 the difference between survivors and nonsurvivors reached statistical significance. Protein C plasma levels were low in both groups. Levels on day 7 were even lower as compared with day 1 in nonsurvivors. Survivors presented low levels only on days 1 and 4. On days 4 and 7, levels in survivors and nonsurvivors became significantly different (Fig 1, middle panel). Protein S levels tended to be low in both groups, but they did not reach statistical significance. Levels on day 7 were higher than on day 1 both in survivors and nonsurvivors. The TATs were high in both groups on days 1 and 7. Levels in nonsurvivors were significantly higher than in survivors on day 7 (Fig 1, lower panel). In both groups, levels on day 7 were lower than on day 1. D-dimer levels were high in both groups throughout the study period. No significant differences between survivors and nonsurvivors were observed.

Plasminogen levels were low on days 1, 4, and 7 in nonsurvivors. However, survivors presented low levels only on day 1. Levels on days 4 and 7 in this group were significantly higher than on day 1. On day 4, the difference between both groups was statistically significant. α2-Antiplasmin levels were not significantly different from the control group in any of the patient groups. The ratio between plasminogen and α2-anti-

\[\text{Figure 1. Changes in coagulation parameters in patients with sepsis on days 1, 4, and 7 after diagnosis. White circles = survivors; black circles = nonsurvivors; TAT = thrombin-antithrombin complexes; dashed lines = median values of the control group. * = p < 0.05 for the comparison with the control group; † = with the first day; and ‡ = between survivors and nonsurvivors. Values are medians.}\]
plasmin was initially low in both groups. However, survivors showed significant elevations thereafter. The difference between survivors and nonsurvivors was statistically significant on day 7 (Fig 2, upper panel).

The PAI-1 levels were high in both groups throughout the study period. However, levels in survivors on days 4 and 7 were significantly lower than on day 1 (Fig 2, middle panel). The t-PA levels were high in nonsurvivors on days 1, 4, and 7 (Fig 2, lower panel). However, survivors showed high levels only on day 1. Levels on day 4 and 7 in survivors were not significantly different from the control group and were significantly lower than on day 1. Values on days 4 and 7 were significantly different between survivors and nonsurvivors. The u-PA levels were high in both survivors and nonsurvivors. On day 7, levels were higher in nonsurvivors.

**Discussion**

Our results are consistent with a profound hemostatic derangement in patients with sepsis, characterized by coagulation activation and fibrinolysis activation and inhibition. Nonsurvivors presented signs suggestive of a more marked activation of coagulation and a stronger inhibition of fibrinolysis than survivors. Differences between survivors and nonsurvivors were not apparent at the time of hospital admission. Only serial measurements revealed a different profile depending on the outcome.

Coagulation activation and the subsequent diffuse intravascular deposition of fibrin have been implicated as an etiologic factor in the organ dysfunction and failure in sepsis. The severity of some abnormalities in the coagulation and fibrinolytic systems is related to outcome. It has been suggested that monitoring the degree of hemostatic abnormalities by serial measurements during the clinical course of these parameters could have diagnostic, prognostic, and therapeutic implications.

It is well known that coagulation activation occurs in sepsis. However, the complex interaction between endotoxin and acute proinflammatory mediators with hemostasis and endothelial cells is not completely understood. Both the intrinsic and extrinsic pathways are involved. It is known that sepsis and ARDS are associated with contact system activation. Endotoxin can induce activation of factor XII, and endothelial injury, with exposure of collagen and other components of the vascular basement membrane, can also lead to factor XII activation. On the other hand, endotoxin-mediated release of interleukin 1 and tumor necrosis factor may induce the expression of tissue factor and adhesive molecules on endothelial cells surface. Tissue factor can initiate and propagate coagulation pathways on endothelial cell surfaces and lead to the deposition of fibrin.

The vWF:Ag, important in platelet adhesion to exposed collagen after injury to endothelial cells, is also released by exposure to endotoxin and interleukin 1, as well as by thrombin and fibrin. Endotoxin also induces a decrease in thrombomodulin, an endothelial cell surface protein that modulates activation of the circulating anticoagulant protein C.

In our series, both survivors and nonsurvivors presented signs of activation of the coagulation process. Low protein C and antithrombin III levels coupled with high D-dimer and TAT levels indicate that coagulation is actively taking place with consumption of coagulation inhibitors as well as generation of fibrin. All our patients were treated with low molecular weight heparin as routine prophylaxis for embolic disease. Although this regimen could cause consumption of antithrombin III, the procoagulant and relative hypofibrinolytic state subsequently reported in our series would be even more marked in the absence of this treatment. Furthermore, since both survivors and nonsurvivors were treated equally, differences between the two groups are sustainable.
Hesselvich et al. found that on the day following hospital admission patients with septic shock had lower antithrombin III and protein C levels than those with infection but without shock. The same group reported signs of more intense activation of coagulation in patients with septic shock as compared with those with infection without shock. Differences between survivors and nonsurvivors were not statistically significant. These findings were confirmed by Phillipe et al. who also reported signs of more marked activation of coagulation in nonsurvivors of septic shock as compared with survivors on the day of hospital admission. In our series, nonsurvivors had a more marked activation of the coagulation system expressed by lower protein C and antithrombin III levels, and higher TAT concentration. Only survivors showed a pattern of progressive normalization of protein C and antithrombin III. Like other studies, the first determination on day 1 did not detect significant differences in protein C and antithrombin III.

The fibrinolytic profile presented by our patients was characterized by elevation of both activators and inhibitors of fibrinolysis, with signs of plasmin generation. Plasminogen levels were low in both groups. Nonsurvivors tended to have even lower levels, whereas survivors showed a trend toward normalization. The decrease in plasminogen levels could be due to decreased synthesis. However, the higher than normal concentration of several other proteins such as α2-antiplasmin and fibrinogen suggests that the low levels of some of the proteins studied cannot be explained only by a decreased global protein synthesis. The previous findings could be better explained by an imbalance between plasminogen synthesis and consumption. Nonsurvivors would have a limited (absolute or relative) ability to meet the increased consumption of plasminogen and maintain levels comparable to those of survivors.

α2-Antiplasmin is the main plasma plasmin inhibitor. Its plasma concentration rapidly falls as plasmin is generated from plasminogen in plasma. However, despite markedly low plasminogen levels, α2-antiplasmin concentration remained normal. The initially low plasminogen/α2-antiplasmin ratio became normal in survivors, while nonsurvivors had a persistently low ratio. We speculate that normal α2-antiplasmin concentration and a low plasminogen/α2-antiplasmin ratio could indicate that plasmin formation takes place mainly at sites of fibrin generation, so that circulating α2-antiplasmin levels remain normal.

High PAI-1 levels have been found in different clinical conditions related to thrombotic phenomena as well as in human sepsis. Some studies have related high PAI levels with a poor prognosis in septic shock. There is evidence for an important functional significance of the rise in PAI levels in sepsis. It has been shown that the decreased fibrinolytic activity in normal subjects given endotoxin is mainly due to the appearance of PAI-1. Given the above body of information, it has been suggested that pharmacologic modification of PAI release could be of therapeutic interest in patients with severe sepsis.

Higher levels of PAI antigen and t-PA activity in nonsurvivors of septic shock have been reported. Phillipe et al. found that on the day of hospital admission, this parameter did not discriminate survivors from nonsurvivors. In our experience, serial determinations were needed to detect differences between survivors and nonsurvivors. The PAI levels were markedly high in both groups. Only survivors had a significant decrease compared with their initial value. These results suggest that there is a more strongly inhibited fibrinolysis in nonsurvivors of septic shock as compared with survivors. Only serial measurements allowed us to detect those differences.

Previous studies have found high t-PA antigen levels in human sepsis. Interestingly, t-PA activity was undetectable in one study, probably due to the even higher elevation of PAI. In our patients, t-PA levels were increased in survivors only on day 1, and subsequently they returned to normal. Nonsurvivors had persistently high levels with no trend toward normalization during the study period. t-PA in septic patients is strongly inhibited by the very high levels of PAI. It has been reported that patients with disseminated intravascular coagulation of different etiologies who present with multiple organ failure have more marked elevations of t-PA/PAI complexes than those who do not develop multiple organ failure. Patients with uncontrolled disseminated intravascular coagulation usually have severe bleeding. However, patients with severe sepsis manifest biologic signs of disseminated intravascular coagulation and usually die of multiple organ failure very often with no signs of external bleeding. It can be hypothesized that the high PAI levels in patients with severe sepsis determine an imbalance in the fibrinolytic response favoring fibrin deposition. Although our data do not provide direct evidence that nonsurvivors have a decreased ability to lyse fibrin, the finding of persistently high PAI-1 concentration suggests an impaired fibrinolytic ability as compared with survivors in the context of a more marked activation of coagulation (lower protein C and antithrombin III levels, and higher TAT concentration).

Little is known about the role of other plasminogen activators such as u-PA. It is believed that endothelial cell-mediated fibrinolysis is dependent on t-PA, whereas u-PA is probably more important in modulation of biologic processes requiring extracellular proteolysis. Only recently, it has been shown that
u-PA is increased in human sepsis, and that this parameter is able to discriminate survivors from nonsurvivors. We found high levels of u-PA in both survivors and nonsurvivors. In our experience, however, those levels discriminated both groups only on day 7.

As a marker of endothelial stimulation and injury, vWF:Ag levels were markedly high in our patients. However, this level did not discriminate survivors vs nonsurvivors. vWF:Ag levels are known to be elevated in patients with acute respiratory failure. It has also been shown that patients with nonpulmonary sepsis who subsequently develop ARDS have higher levels of vWF:Ag than those who do not develop ARDS. The lack of enough patients with nonpulmonary sepsis in our series did not allow comparison with those results. Although we were not able to identify a particular pattern in the time course of vWF:Ag levels, pooling together all determinations allowed us to detect statistically significant higher levels in patients with ARDS as compared with those who did not have ARDS, suggesting a more marked activation of endothelial cells in this condition. This finding indicates that sepsis is accompanied by biochemical signs of endothelial cell estimation, which is more marked in patients with ARDS.

In summary, clinical sepsis is characterized by coagulation activation and elevation of both activators and inhibitors of fibrinolysis. We provide evidence suggesting that nonsurvivors have a stronger activation of coagulation and a more marked inhibition of fibrinolysis than survivors, with the consequent decreased ability to lyse fibrin. The profile described herein in septic patients studied during one week indicates that most of the differences between survivors and nonsurvivors may not become evident until several days after the diagnosis is established or if only isolated measurements are performed. Among the parameters measured in our study, changes in antithrombin III, plasminogen/α2-antiplasmin ratio, protein C, and PAI-1 levels were those that more characteristically varied differently in the group of survivors as compared with nonsurvivors. It remains to be established whether pharmacologic intervention to modify that profile, ie, inhibiting PAI secretion, administering activated protein C, or anti-tissue factor antibodies alters the outcome of these patients.

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