Intensive Care Med (1993) 19:S8–S15

Intensive Care Medicine

Coagulation disorders in septic shock

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Abstract. Abnormalities in coagulation and fibrinolysis are frequently observed in septic shock. The most pronounced clinical manifestation is disseminated intravascular coagulation. Recent studies in human volunteers and animal models have clarified the early dynamics and route of activation of both coagulation and fibrinolytic pathways. In healthy subjects subjected to a low dose of either endotoxin or TNF an imbalance in the procoagulant and the fibrinolytic mechanisms is apparent, resulting in a procoagulant state. Also in patients with septic shock a dynamic process of coagulation and fibrinolysis is ongoing with evidence of impaired fibrinolysis. These abnormalities have prognostic significance; the extent of disturbances of coagulation and fibrinolysis is related to the development of multiple organ failure and death.

Key words: Sepsis – Coagulation – Fibrinolysis – Septic shock

Coagulation disorders and abnormalities of fibrinolysis are common in septic patients. Its most pronounced manifestation is disseminated intravascular coagulation (DIC), a process characterized by microvascular thrombosis, consumption of platelets and coagulation proteins and stimulation of the fibrinolytic system. Consumption of platelets and coagulation factors sometimes results in clinically apparent hemorrhagic disorders. The impressive extreme of the clinical spectrum of DIC is purpura fulminans with hemorrhagic necrosis and peripheral gangrene usually, but not exclusively, caused by meningococcal infection.

Sepsis is the most common cause of acute DIC and this syndrome is a frequent complication of severe sepsis. The reported incidence of DIC in sepsis varies greatly mainly because diagnostic criteria and definitions for DIC and sepsis are not uniform. Even with rather rigid criteria for DIC its incidence may be as high as 70% in patients with septic shock [1, 2]. Patients with septic shock who develop DIC have a higher mortality than those who have no signs of DIC [1, 2]. Some clinical observations indicate that DIC is an important pathogenetic factor for the development of multiple organ failure [1]. Widespread microvascular thrombosis in various organ systems is a common feature of lethal septic shock [3] and may considerably contribute to organ dysfunction [4, 5].

Coagulation and fibrinolysis

Recent evidence suggests that the classical model of an intrinsic and an extrinsic pathway, both resulting in factor X, V, and prothrombin activation, is no longer tenable. Factors VIII, IX, and XI, formerly part of the intrinsic pathway, should be considered as amplification factors of the extrinsic pathway (Fig. 1). Factor XII does not seem to play a significant role as a coagulation factor in vivo, but rather participates in the kallikrein-kinin pathway, which can be activated by negatively charged surfaces. It has been shown that bradykinin, a product of the contact (= kallikrein-kinin) system, is an important mediator of hypotension during sepsis, and that inhibition of its formation attenuates manifestations of septic shock [6]. Supporting the notion that the contact system of coagulation plays little role in DIC of sepsis is that inhibition of factor XII in septic baboons has no effect on the coagulative changes in these animals [7]. The extrinsic pathway is initiated by tissue factor, a normal constituent of the surface of non-vascular cells and stimulated monocytes [8]. The exposure of cell surfaces expressing tissue factor to the plasma proteins leads to the binding of factor VII to tissue factor. The complex of activated factor VII (factor VIIa) and tissue factor activates factors IX and X and a sequence of proteolytic activation results in the formation of thrombin from prothrombin. Thrombin cleaves fibrinogen yielding monomeric fibrin which then polymerizes to form the fibrin clot [8].

Regulatory mechanisms of coagulation, which prevent coagulation from becoming generalized, include the natural inhibitors of clotting: antithrombin III (AT III),

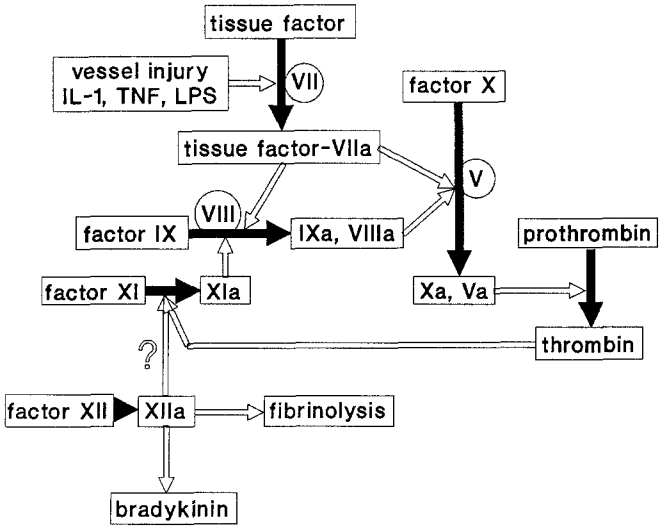

Fig. 1. Revised coagulation cascade. Activation is started with exposure of tissue factor and subsequent activation of factor VII. Activated factor VII (VIIa) activates factor X, which together with factor Va converts prothrombin into thrombin. Amplification of this primary pathway occurs at two levels: 1) the tissue factor-VIIa complex may also activate factor IX which together with factor VIIIa can activate additional factor X; 2) thrombin may activate factor XI, which in turn activates factor IX. In vitro, factor XI can be activated by factor XIIa, but it is questionable whether this occurs in vivo. Note that the role of calcium-ions, phospholipids and the conversion of cofactors V and VIII are not depicted

the protein C (PC)-protein S (PS) system and the extrinsic pathway inhibitor. AT III binds to thrombin generated during the clotting process to form thrombin-antithrombin (TAT) complexes (whereby thrombin activity is neutralized) and also inactivates other activated blood clotting enzymes moving away from a growing clot [8]. The formation of complexes is accelerated by heparin. While thrombin free in solution promotes clotting by its actions on fibrinogen and its role in platelet activation, complexes of thrombin with the endothelial-membrane receptor thrombomodulin activate protein C. This activated PC proteolytically inactivates the active cofactor forms factor V and VIII, thereby rapidly slowing blood clotting [8]. PC also enhances fibrinolysis by neutralizing plasminogen activator inhibitor-1 (PAI-1) [8]. Protein S serves as a cofactor for activated protein C and exists in human plasma in two forms: as free protein and as inactive form complexed with C4b-binding protein (C4BP). Protein S functions by enhancing the cell surface anticoagulant activity of activated PC [9]. Deficiency of any of these natural inhibitors is associated with thromboembolic disease, illustrating their important role in regulating the clotting system.

During strong activation of coagulation such as occurs during disseminated intravascular coagulation clotting factors and also inhibitors are rapidly consumed. Their half-life is decreased in such clinical conditions.

The fibrinolytic system plays an important role in regulating the formation and removal of formed microthrombi. Fibrinolysis is an endogenous mechanism of the organism to preserve the microcirculation from irreversible damage. Fibrinolysis is initiated by the release of tissue type plasminogen activator (t-PA) from vascular endothelium which converts plasminogen into the active enzyme plasmin that degrades fibrin in the thrombi. Plasmin levels are regulated by the natural inhibitor α-2 antiplasmin (α_2AP) which binds plasmin to form plasmin-α_2AP (PAP) complexes whereby plasmin is neutralized. PAP complexes in plasma are a direct indicator of in vivo plasmin generation. The level of active t-PA in blood is regulated in part by PAI-1 which binds to and inactivates t-PA. Therefore, elevated levels of PAI-1 suppress fibrinolysis. On the other hand, activated PC is not only a potent anticoagulant but also enhances fibrinolysis by binding to and neutralizing PAI-1, although at a much slower rate than t-PA. Endothelial cells are capable to release PAI-1 but in human blood the majority of PAI-1 is associated with platelets and released upon platelet aggregation [10].

In vitro studies

The vascular endothelium which synthesizes and releases promotors and inhibitors of blood coagulation and provides a surface for the attachment of cells, is one of the principle targets in sepsis. Most of the clinical symptoms of septic shock are believed to be mediated by the release of a wide array of host response mediators among which cytokines seem to play a pivotal role. In Gram-negative sepsis this release is mediated by endotoxins present in the outer membrane of Gram-negative bacteria. In vitro studies have demonstrated that endotoxin [11, 12], interleukin-1 [13] and TNF [14–16] enhance tissue factor expression on human endothelial cells, a process that takes a few hours. Several observations indicate that de novo synthesis of tissue factor is involved. Endotoxin [11], IL-1 [17], and TNF [17–19] can decrease thrombomodulin expression in such a model. TNF suppresses transcription of the thrombomodulin gene [19] and leads to internalization and degradation of thrombomodulin from the surface of endothelial cells [18].

Incubation of vascular endothelial cells with endotoxin [20, 21], IL-1 [20] or TNF [22] results in a suppression of their fibrinolytic capacity by decreasing t-PA activity. In contrast, however, urokinase type plasminogen activator (u-PA) production by endothelial cells is stimulated by TNF and IL-1 [23]. Cultured human endothelial cells also release PAI-1 in response to endotoxin [20, 22, 24], TNF [22, 23] or IL-1 [20]. These findings indicate that endotoxin directly or indirectly through the action of TNF and IL-1 can modulate endothelial cell hemostatic properties in such a way that the endothelial surface becomes procoagulant and fibrinolysis is counteracted. Moreover, fibrin and thrombin formed during coagulation are potent inducers of t-PA and PAI-1 release by endothelial cells [25, 26]. Thrombin also stimulates the production of u-PA [27]. The net effect of thrombin, however, appears to be a decrease in fibrinolysis [25]. It has been suggested that thrombin acts in this respect by inducing another effector such as interleukin-1 [28]. Thrombin has anticoagulant effects which include stimulation of prostacyclin secretion and activation of PC [29] as well as a

number of procoagulant effects on endothelial cells including release of tissue factor, factor VIII, von Willebrand factor and platelet activating factor [29]. Studies in cultured endothelial cells obviously cannot be related directly to in vivo situations but rather present possible mechanisms of regulation that can occur in vivo.

Studies in healthy subjects

In order to clarify the route and early dynamics of both coagulation and fibrinolysis pathways, studies in healthy volunteers subjected to low intravenous doses of endotoxin or TNF seem rewarding. Although, admittedly, only low doses can be administered, such a model can be used to unravel the sequences of activation of coagulation and fibrinolysis in humans. A bolus injection of endotoxin elicits an increase in body temperature and pulse rate and a mild decrease in blood pressure accompanied by an influenza-like syndrome [30, 31], a fall in leukocyte count followed by leukocytosis [31] and a transient fall in platelet count [32] which may, however, be absent [31]. An early rise in levels of TNF followed by an increase in IL-6 and IL-8 levels is a constant feature of this model [31, 33, 34]. Detection of IL-1 after endotoxin bolus injection has been more elusive and several groups have been unable to detect significant changes in circulating IL-1 [31, 33], although low levels of IL-1 bioactivity have been described [34].

Following the transient increase in TNF levels an increase in prothrombin fragments (F1+2) and levels of TAT complexes, indicative of the activation of the common pathway of coagulation, is first observed about 2 h after endotoxin administration [31]. This activation of the common pathway of coagulation takes place in the absence of demonstrable contact system activation [31], although this system can be activated using higher doses of endotoxin [35]. In this model von Willebrand factor antigen is also released [30, 31]. The fibrinolytic system is activated within 1 h after endotoxin as evidenced by a rapid rise of t-PA antigen [30, 31] and activity [30] and a rise in levels of PAP complexes [30, 31]. t-PA antigen levels gradually fall after about 2 h and simultaneously PAI-1 levels increase (while t-PA activity abruptly falls to nearly undetectable levels) to reach a maximum by 5–6 h. Thus, during this period, an apparent procoagulant state is created as the initial fibrinolytic response is counteracted by the subsequent release of PAI-1.

Studies using a recombinant TNF bolus injection in healthy subjects have shown that this cytokine induces an early and transient increase in factor X activation peptide and a significant, more gradual increase in F1+2 levels peaking at 4–5 h, indicating activation of the common pathway of coagulation [36]. No activation of the intrinsic pathway of coagulation could be demonstrated. Also the fibrinolytic system is activated as evidenced by an early and brief increase in overall plasminogen activation (PA) activity peaking at 1 h and associated with a rise in antigenic levels of urokinase-type plasminogen activator (u-PA) and in particular of t-PA. This is paralleled by a transient elevation of levels of D-dimers and PAP complexes and a decline in α_2-antiplasmin activity [37]. During the first hour PAI-1 antigen levels remain unchanged but then rapidly increase coinciding with a decrease in PA activity [37].

Thus, TNF induces a rapid activation and subsequent inhibition of fibrinolysis in healthy subjects. Similar observations have been reported in cancer patients in whom continuous infusion of TNF resulted in activation of both coagulation and fibrinolytic pathways [38, 39].

As in the endotoxin studies fibrinolysis is also stimulated in this model before significant thrombin generation can be detected in plasma and fibrinolysis is already offset when prothrombin activation becomes maximal. In both models, therefore, there seems to exist a remarkable imbalance in the procoagulant and fibrinolytic mechanisms, associated with a procoagulant state several hours after the challenge. The TNF-induced changes are comparable to those of endotoxin but are detected 1–2 h earlier. This interval is identical to the time in which serum TNF reaches peak values after endotoxin injection. These observations strongly suggest that TNF is a major factor in inducing sepsis-associated abnormalities in coagulation and fibrinolysis. Although endotoxin and TNF in vitro can induce endothelial release of several factors involved in coagulation and fibrinolysis (vide supra) these processes are relatively slow and cannot explain the rapid responses observed in the in vivo studies. Therefore, other mechanisms must be involved. These studies do not elucidate the exact mechanism underlying the in vivo effects of endotoxin or TNF. They have, however, markedly increased our insight into the early dynamics of coagulation and fibrinolysis in low grade and subclinical activation of these systems and have identified potentially important pathophysiologic mechanisms. The precise description of the sequence of activation and regulation of coagulation in these models has a bearing on our understanding of coagulation abnormalities as observed in patients with severe sepsis.

Studies in septic patients

In patients with sepsis and septic shock signs of activation of the coagulation system occur frequently as judged from common hemostatic variables. These changes are usually more pronounced in septic shock than in sepsis without compromized circulation. Coagulation tests may show prolonged clotting times indicating consumption of clotting factors, a process which is most pronounced in DIC [1, 40, 41]. Fibrinogen levels are usually elevated in uncomplicated sepsis [41–43] and may vary widely in septic shock [40] but are usually somewhat lower than in sepsis [42]. In DIC levels can be distinctly reduced [1]. Platelet count in septic shock is usually reduced due to a variety of mechanisms. Lower levels of factor VII and normal levels of factor V have been found in sepsis and septic shock with a decrease of prothrombin complex [42, 44]. When DIC supervenes levels of factor V decline [1, 2].

In recent years newer laboratory techniques for the assessment of ongoing coagulation (and fibrinolysis) have allowed us to study these processes in more detail. Elevated levels of TAT complexes, a sensative indicator of activation of the coagulation system have been found in patients with sepsis and septic shock [43–45]. In a series of 38 patients with septic shock we found elevated levels of TAT complexes in all but one patient on admission (de Groot et al., manuscript in preparation). Levels were significant higher in non-survivors than in survivors.

The dynamics of coagulation have been studied in the subhuman primate model. Baboons subjected to a sublethal or lethal concentration of *E. coli* demonstrated elevated circulating TAT complexes as early as 30 min after the challenge followed by a continuous rise, the highest values being observed after a lethal dose [46]. Although in vitro studies have shown that cytokines are able to alter the surface of endothelial cells from an anticoagulant into a procoagulant state, in this model cytokines appear in the circulation after 60 min [47]. Although early local effects of cytokines cannot be excluded, this finding suggests that mechanisms other than the effects of cytokines could be involved in the initiation of coagulation. Levels of von Willebrand factor antigen, which is produced by endothelial cells and important for platelet adhesion, are elevated both in patients with uncomplicated sepsis and in patients with septic shock [42]. They stabilize in survivors and continue to rise in non-survivors becoming significantly higher in non-survivors compared with survivors in the days following admission [42].

In patients with sepsis and septic shock, increased levels of circulating factor XIIa-C 1 inhibitor, and kallikrein-C 1 inhibitor complexes have been demonstrated, but only in a minority [48]. This indicates activation of the intrinsic pathway (contact system) of coagulation at least in some of these patients. This is corroborated by the low levels of factor XII and of prekallikrein as found in patients with sepsis [40–42, 48]. Factor XII levels are lowest in patients with septic shock [42, 48] and in non-survivors [42] and related to severity of disease [41]. In surviving patients, values gradually return toward normal but they remain low in non-survivors [40]. Prekallikrein levels are lowered in sepsis and significantly lower in septic shock [42], although such differences have not been found in another study [48]. Levels may [40] or may not [42] significantly differ between survivors and non-survivors and return gradually toward normal in survivors [40].

Nevertheless, there is doubt whether contact activation is an important mechanism in coagulation and DIC in sepsis [6]. Attenuation of the intrinsic pathway by administration of anti-factor XII monoclonal antibodies in the baboon model had no effect on the activation of coagulation [7]. Tissue factor expressed on the surface of endothelial cells is supposedly a major mechanism in initiating coagulation in sepsis. It has been demonstrated that endothelial cell injury by activated granulocytes may increase the exposure to tissue factor [49]. Also expression of tissue factor on monocytes and macrophages can contribute in this process. Circulating monocytes isolated from blood from patients suffering of meningococcal disease also demonstrate elevated tissue thromboplastin [50]. Highest values are found in non-survivors [50]. It seems likely that activated monocytes play a role in the generation of thrombin as a highly positive correlation has been found between the number of monocytes and the levels of TAT complexes in patients with sepsis [45]. In severely leukopenic patients who developed sepsis no clear evidence of thrombin generation has been demonstrated [45]. Direct evidence for an essential role for tissue factor in septic shock has been provided by studies in a relevant primate model of septic shock. Infusion of small amounts of anti-tissue factor monoclonal antibodies protected baboons from the lethal effects of a lethal dose of *E. coli* and attenuated the coagulopathy seen in this model [51].

Levels of natural inhibitors of coagulation are markedly altered. Several studies have demonstrated that ATIII levels are lowered during severe infection [44, 52], sepsis [41–43, 52] and septic shock [1, 40, 42, 44, 52] even in the absence of clinically manifest defibrinating DIC [44]. In the latter group the most pronounced decrease of ATIII levels is found [2, 42, 44]. In patients with septic shock complicated by DIC, initial levels of ATIII are almost uniformly severely decreased. They are related to outcome: levels are significantly lower in nonsurvivors than in survivors [1, 2, 40]. In one study [1] an initial level for ATIII $< 50\%$ had a good prognostic value for prediction of subsequent death [specificity 0.76, sensitivity 0.96]. Serial measurements have shown that in survivors a slow spontaneous recovery of ATIII levels to normal occurs while in non-survivors levels usually remain low [1, 40, 53].

In patients with meningococcal infections those with the fulminant form had the lowest values associated with the highest levels of endotoxin [53]. Low or falling levels of ATIII in patients with infections are associated with an increased risk of sepsis and death [54].

The main mechanism by which ATIII activity declines in sepsis is acute consumption during the process of coagulation. Other mechanisms may contribute however. Although a decreased ATIII synthesis may be a factor in liver failure, there is no clear evidence this is a major factor in sepsis, although it may contribute in patients with sepsis-induced liver function abnormalities. Also, increased leakage from the intravascular compartment could be implicated. Proteolytic inactivation of ATIII might be an important mechanism [55]. ATIII can be rendered nonfunctional as an inhibitor of clotting enzymes as a result of limited heparin-dependent cleavage by elastase released from activated neutrophils [56]. In our series of 38 patients with septic shock we observed a decreased level of functional ATIII (compared to normals). Non-surviving and surviving patients had similar levels ($43 \pm 11\%$ versus $44 \pm 11\%$, respectively). Antigenic levels of ATIII were less decreased in these septic patients ($74 \pm 24\%$ of normal), indicating the presence of non-functional ATIII. This non-functional ATIII accounted for 33% (mean) of the total amount of ATIII. The reason for this inactivation of ATIII in these septic patients is not clear, and needs further investigation.

Protein C levels are decreased in patients with severe infection [1, 44], sepsis [41–43, 52] and septic shock [1,

44], the lowest values being found in the latter group [42] even in the absence of clinical DIC [44]. Similar findings have been observed in children [2, 53] and adults [58] with severe infectious purpura. PC levels are lowest in patients who exhibit DIC [2] but may be similar [59]. Initial levels of PC may be lower in non-survivors than in survivors [1, 2] or may not differ between these groups [42, 53]. In septic patients with DIC there is an acute, severe and prolonged decrease in PC activity which persists in non-survivors [1, 53]. In survivors PC levels gradually normalize in the course of days [1, 53]. A major mechanism for depressed levels of PC is presumably persistent consumption during the septic process. In vitro studies have shown that cytokines such as TNF and IL-1 can induce downregulation of thrombomodulin on endothelial cells which interferes with activation of PC. Although differences in PC activity and PC antigen in plasma have been observed which may indicate complexing with a plasma inhibitor and loss of activity [57] such differences have not been found in several other studies [1, 2, 58].

In patients with severe infection levels of total and free protein S and C4b-binding protein are normal or even slightly elevated [44]. In septic shock levels may be normal [44] or lowered [1]. The decline in PS levels is in general less pronounced than the decrease in ATIII or PC levels. In children and adults with severe infectious purpura lowered total levels of protein S have been demonstrated [2, 58]. Patients who developed DIC had significantly lower levels than patients who had no signs of DIC, while survivors had significantly higher levels than non-survivors [2]. The decrease in ATIII, PC and PS levels is consistent with a prolonged consumption on inhibition at the endothelial site and may explain a sustained procoagulant state [1].

Studies in non-human primates given a lethal dose of *E. coli* have demonstrated a significant fall in the level of ATIII [60]. Infusion of relatively large amounts of ATIII reduced the intensity of the coagulopathic and cell injury responses and prevented death [60]. Experimental studies in baboons have also demonstrated that infusion of activated PC prevented the coagulopathic, hepatotoxic and lethal effects of infusion of lethal concentrations of *E. coli* micro-organisms [61]. In addition, blocking PC activation in vivo using an antibody against PC resulted in a more severe pathologic response to sublethal concentration of *E. coli* which can be prevented by infusion of activated PC [61]. C4bBP directly inhibits PS activity giving rise to an acquired functional PS deficiency. C4bBP infusion in baboons challenged with a sublethal dose of *E. coli* exhibited rapid consumption of fibrinogen, elevated TNF levels, organ damage and they ultimately died, largely exaggerating the response as seen with *E. coli* alone during which no TNF could be detected in the plasma [62]. These studies illustrate the importance of natural inhibitors in the pathophysiology of septic shock. These studies would also be consistent with the hypothesis that coagulation and fibrinogen consumption might augment the inflammatory response. However, infusion of factor Xa blocked in the active centre (which competes with factor Xa for binding to factor Va) completely inhibited the coagulant response of *E. coli* infusion in the same model while the appearance of TNF in plasma, the hemodynamic changes and the lethal effects were not prevented [63]. These studies suggest that these natural inhibitors attenuate the inflammatory response by some other mechanism than blocking fibrin formation.

Activation of coagulation is accompanied by activation of fibrinolysis. In the baboon model levels of t-PA complexes start to rise within 30 min after the administration of *E. coli* and are significantly higher after a lethal dose than after a sublethal dose [46]. In patients with severe infection t-PA activity has not been found elevated although levels of t-PA antigen showed elevated values [52]. In patients with sepsis and septic shock levels of t-PA antigen are markedly elevated on the day of admission [41, 52]. In one study also t-PA activity was elevated [52], but in another no free t-PA activity could be detected [41]. Levels of t-PA antigen are related to severity of disease as measured with the APACHE score [41]. Although no differences have been found in t-PA antigen between survivors and non-survivors, levels of t-PA activity were significantly different, being higher in non-survivors [52]. Also u-PA antigen is markedly elevated in sepsis and septic shock but not in patients with severe infection [52]. Levels on admission are significantly higher in non-survivors than in survivors and they remain elevated for prolonged periods [52]. Plasminogen levels are within the normal range in patients with sepsis but lowered in septic shock [41, 42]. In survivors levels gradually increase while in fatal septic shock persistent low values are observed [42]. Lower values have been found in patients with fulminant meningococcal septic shock than in patients with less severe meningococcal infection [64]. No differences could be established in initial values between survivors and non-survivors [42, 64].

Levels of α_2-antiplasmin are usually not altered during sepsis [41–43, 45] but are low in septic shock [42, 64]. Although initial values may [64] or may not [42] be different between survivors and non-survivors, in the days following admission levels are significantly lower in non-survivors.

In many patients with severe sepsis-circulating PAP complexes can be detected [43, 45]. In our study we found elevated PAP complexes in 35 out of the 38 patients with septic shock (de Groot et al., manuscript in preparation). However, in one study, in various disease entities associated with DIC the lowest PAP levels were found in patients with sepsis indicating an ineffective fibrinolysis in this group [43]. It is highly likely that fibrinolysis is strongly inhibited by the release of PAI-1 into the circulation. Studies in baboons have shown that upon a challenge with *E. coli* PAI-1 levels appear after one hour and levels progressively rise [46]. In animals given a sublethal concentration of *E. coli* PAP levels declined in association with the increase in PAI-1 levels suggesting that this inhibitor of plasminogen activation is responsible for attenuation of fibrinolysis.

PAI-1 levels in patients with sepsis are usually within normal limits or moderately elevated [42]. Elevated levels have been found in patients with severe infection [52]. In septic shock values are in most patients markedly elevated [41, 65]. Initial levels in patients who die are significantly

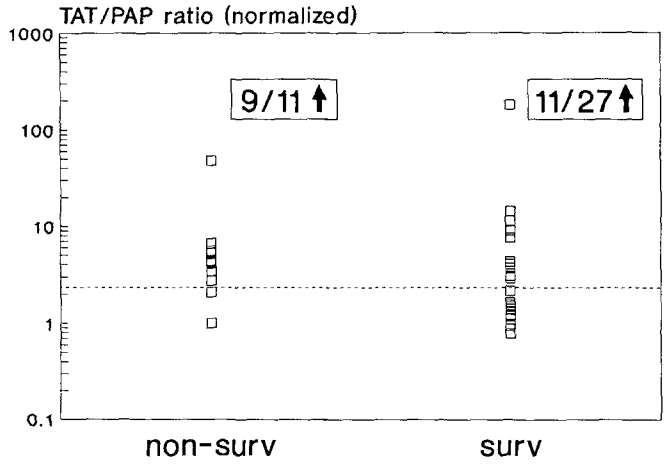

Fig. 2. Ratio of TAT/PAP complexes in patients with septic shock. Levels are significantly higher in non-survivors than in survivors ($p < 0.05$)

higher than in survivors [42, 64] or may be similar [52], but increase progressively in the former [42]. In contrast, it was demonstrated in fulminant meningococcal septic shock that levels of PAI-1 peaked on or shortly after admission, declining rapidly thereafter [64]. A correlation with severity of disease has been reported [41]. In one study values for survivors and non-survivors were statistically not different, but PAI-1 levels were significantly higher in patients dying within one week after the onset of septic shock than in survivors [65]. Duration of septic shock prior to measurement has no influence on PAI-1 levels indicating that levels are already markedly elevated early in septic shock [65].

In most patients with severe sepsis a strong inhibitor of fibrinolysis is present in the circulation which explains why t-PA activity is only mildly elevated in contrast to t-PA antigen or even absent [41, 52]. Notwithstanding this antifibrinolytic activity levels of cross-linked fibrin degradation products (D-dimers) are elevated [41, 42, 45]. They are higher in septic shock then in sepsis [42] and indicate that (some degree of) fibrinolysis is still ongoing. It has been suggested that, although t-PA activity in the systemic circulation might be inhibited, t-PA is still active in the microcirculation because of its high affinity to fibrin and that there is fibrinolysis in the microcirculation resulting in elevated D-dimers levels in plasma [41]. Although levels are markedly elevated, PAI-1 may be partly non-functional, due to rapid conformation of active PAI-1 into a latent configuration [66–68], proteolytic or chemical inactivation of PAI-1 by non-target proteases e.g. elastase and plasmin [68] or oxygen free radicals [69, 70]. Such mechanisms may interfere with its antifibrinolytic activity.

From these clinical studies the picture emerges that in sepsis and septic shock a dynamic process of coagulation and fibrinolysis is ongoing while the latter is counteracted with resulting impaired fibrinolysis. In our group of patients with septic shock we found an elevated ratio of TAT/PAP complexes in 20 out of 38 patients. This ratio was significantly higher in non-survivors than in survivors (Fig. 2). In a study of various disease states associated with DIC the highest TAT/PAP ratios have been found in septic patients [45].

These abnormalities have major pathophysiological implications and seem to be correlated with mortality. In particular in non-survivors the fibrinolytic capacity seems to be insufficient to counteract widespread vital organ microembolization [42]. Abnormalities in fibrinolysis have prognostic significance.

The most striking factor in predicting multiple organ failure and death are the levels of PAI-1 [42, 64, 65] but also levels of vWF ag [42] and α_2-antiplasmin [42, 64] are related to mortality. A better understanding of the complex abnormalities of coagulation and fibrinolysis in sepsis is of importance to design therapeutic strategies to improve outcome in septic shock.

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