INTERFERENCE WITH THE COAGULATION SYSTEM

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In patients with severe sepsis or septic shock, systemic activation of the coagulation system as well as early activation with subsequent inhibition of the fibrinolytic system are common features [1-5]. Using newly developed highly sensitive assays to measure activation products of coagulation, activation of coagulation can be detected even in most patients with uncomplicated sepsis [6]. The most pronounced clinical manifestation of these alterations is disseminated intravascular coagulation (DIC), which is characterized by generation and deposition of fibrin in the microvasculature with widespread microvascular thrombosis in various organs. The progressive inhibition of the fibrinolytic system may ultimately result in impaired fibrin dissolution and aggravate the formation of microthrombi. In addition, depletion of coagulation proteins and platelets, mainly due to the extensive and ongoing activation of the coagulation system may induce severe bleeding complications [7].

Sepsis is the most common cause of acute DIC and DIC is a frequent complication of sepsis with major implications for morbidity and mortality. There is evidence that activation of the coagulation system contributes to the development of organ failure and death [3,5]. The reported incidence and prevalence of DIC in sepsis varies widely depending on type of patients and definitions used to characterize DIC. The prevalence of DIC in patients included in recent large-scale clinical trials in sepsis ranged from 7.5 to 49 % and is generally higher in patients with than in patients without shock [8-11]. In a large prospective study the incidence of DIC in sepsis was 16 %, in severe sepsis 18 % and in septic shock 38 % [12].
IMBALANCE BETWEEN COAGULATION AND FIBRINOLYSIS

In sepsis, coagulation is primarily driven by the tissue factor (TF)-dependent pathway and amplified by activation of various factors of the contact activation-dependent pathway [13]. Several mediators of sepsis (e.g., tumor necrosis factor [TNF], interleukin [IL]-1, endotoxin) can induce TF on endothelial cells and monocytes, which binds to and activates factor VII. Subsequently, the factor VII/TF complex activates a number of proteolytic processes, ultimately resulting in fibrin clot formation. In this process thrombin is generated which binds to antithrombin (AT) to form thrombin-antithrombin (TAT) complexes which are sensitive markers of *in vivo* thrombin generation. Elevated levels of circulating TAT complexes are generally found in septic patients even in the absence of clinically overt DIC [4,5,6,14,15]. These levels are related to the severity of sepsis i.e. highest levels are found in the most severe forms of sepsis [6].

The fibrinolytic system is also activated in sepsis [13]. The importance of this system is its capacity to remove (micro) thrombi and maintain blood fluidity and thereby preserve the microcirculation from irreversible damage. Fibrinolysis is initiated mainly by the release of tissue-type plasminogen activator (t-PA) released from endothelial cells. t-PA converts plasminogen into plasmin which among other proteolytic functions enzymatically degrades fibrin into fibrin degradation products. Fibrinolysis is regulated at two levels. First, t-PA can bind to plasminogen activator inhibitor type I (PAI-1) to form complexes which loose the ability to activate plasminogen. High circulating levels of t-PA antigen can usually be found in septic patients [2,4,16]. In contrast, t-PA activity can often not be detected or is only moderately elevated [2,17], suggesting that t-PA activity is inhibited by PAI-1. Indeed, plasma levels of PAI-1 antigen [1,4,17,18] and PAI-1 activity [2,16,19] are markedly increased in patients with severe sepsis. Second, free plasmin is rapidly bound to circulating *α2-antiplasmin*, thereby forming plasmin-antiplasmin (PAP) complexes which are direct markers of *in vivo* plasmin generation. In many patients with sepsis elevated levels of circulating PAP complexes can be found, indeed indicating activation of the fibrinolytic system [5,15].

Dynamic studies in human volunteers subjected to low dose endotoxin, and in animal models of sepsis, have demonstrated early activation of fibrinolysis before significant thrombin generation can be detected in plasma whereas fibrinolysis is already offset by the release of PAI-1 when thrombin generation becomes maximal [20,21]. So, there is a remarkable imbalance between coagulation and fibrinolysis resulting in a procoagulant state several hours after the challenge. This imbalance can be assessed by the ratio of the levels of TAT