Inflammation and Coagulation

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6.1 Introduction

In critically ill patients, the activation of blood coagulation occurs in parallel with the release of inflammatory mediators, which characterizes systemic inflammatory response syndrome (SIRS) and sepsis and sepsis-related conditions such as severe sepsis and septic shock. As a consequence, the overall hemostatic balance is shifted toward the activation of the coagulation, due to either the activation of the clotting system or the downregulation of the anticoagulant pathways [1, 2].

The inflammatory reaction interacts with the coagulation at different levels, including the elevation of blood fibrinogen levels and the induction of tissue factor (TF) expression on the cell surface of leukocytes. Thrombin can thus promote coagulation, anticoagulation, cell proliferation, and inflammation by triggering some of the responses summarized in Fig. 6.1 [2, 3].

6.2 Coagulation Disturbances in Sepsis

Systemic inflammation during sepsis leads to the generation of proinflammatory cytokines that, among other things, orchestrate coagulation and fibrinolytic activation. Both coagulation activation and downregulation of fibrinolysis are principally regulated by tumor necrosis factor α (TNF-α), interleukin (IL)-1, and IL-6. Moreover, TNF-α influences coagulation activation via the action of IL-6. The cornerstone of the coagulation disorder in sepsis constitutes the imbalance between intravascular fibrin formation and fibrin removal. Severely reduced

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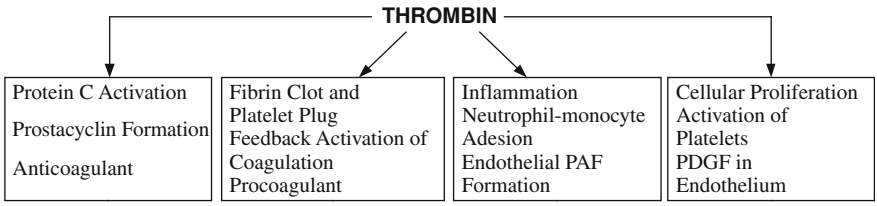

Fig. 6.1 Interaction between coagulation and the inflammatory reaction

anticoagulant capacity and inhibited fibrinolysis are opposed by a massive activation of coagulation, finally leading to overwhelming fibrin formation and consumption of clotting factors and inhibitors as well. Abundant intravascular fibrin formation leads to microvascular thrombosis, which causes widespread ischemic organ damage up to organ necrosis and clinically impresses as widespread skin necrosis and multiple organ dysfunction syndrome [2–4, 5].

Coagulation activation during sepsis is primarily triggered through the Tissue Factor (TF) pathway. In sepsis models, fibrin formation was completely abrogated by blocking this mechanism with anti-TF antibodies and activated factor VII (factor VIIa) inhibiting peptides. Although in a primate model of severe sepsis the contact-phase system was found to be activated, it did not contribute to coagulation activation in sepsis; however, the inhibition of factor XII activation prevented the occurrence of hypotension, indicating that activation of the contact-phase system plays a role for the sepsis-associated hemodynamic changes during sepsis, presumably via the formation of bradykinin [3, 5, 6].

Expression of TF on monocytes and probably on endothelial cells triggers activation of coagulation in sepsis. An additional source of TF might derive from phospholipid fragments originating from activated monocytes, which can be detected in plasma of patients with meningococcal sepsis [5, 7, 8].

After binding to exposed TF, circulating factor VII is activated. The TF/factor VIIa complex then activates factor X to activated factor X (factor Xa), which converts prothrombin to thrombin. These tiny amounts of thrombin formed may activate factor V and factor VIII. Activated factor V (factor Va) enhances the capability of factor Xa to activate prothrombin [7, 9, 10].

However, thrombin generation by the TF/factor VIIa pathway is rapidly abrogated by TF pathway inhibitor, a high-affinity inhibitor of TF/factor VIIa/factor Xa complex present in plasma and on endothelial cells.

However, TF/factor VIIa complex also activates factor IX, which in concert with factor VIIIa takes over the function of TF/factor VIIa to activate factor X, thereby further amplifying the thrombin generation. This amplification of factor X activation by factor IX and factor VIII is important for coagulation in physiologic conditions, as is dramatically demonstrated by the clinical picture of hemophilia A and hemophilia B, which result from deficiency of factor VIII and factor IX, respectively. Thrombin cleaves fibrinogen into fibrin monomers and activates factor XIII, which then covalently cross-links fibrin monomers to form a

stable clot. The thrombin generated by the TF/factor VIIa pathway amplified by factor IX and factor VIII in some conditions is still insufficient to overcome fibrinolysis. To surmount this anticoagulant effect of fibrinolysis, activation of a second amplification loop, in addition to that of factor VIII and factor IX, is necessary. This second loop is triggered when the amount of thrombin generated becomes sufficient to activate factor XI, which then generates factor activated factor IX (IXa), which then activates additional factor X, thereby forming additional thrombin. This amplified factor XI dependent thrombin formation will activate thrombin-dependent fibrinolysis inhibitors, which will cleave off binding sites for plasminogen on fibrin, thereby inhibiting fibrinolysis [2, 5, 11, 12].

Although factor IXa/VIIIa and the activated factor XI amplification loop are considered to be important for coagulation activation in sepsis, the evidence for this is scarce. Thrombin is quickly inactivated by antithrombin by forming thrombin–antithrombin complexes, which are rapidly cleared from circulation. Moreover, thrombomodulin (TM) expressed on endothelial cells binds thrombin and abrogates its procoagulant activity.

The thrombin–TM complex activates protein C. Activated protein C rapidly dissociates from the thrombin TM complex and inactivates factor Va and factor VIIIa, thereby decreasing thrombin generation [5, 7, 13].

The function of the activated protein C system is also severely compromised during sepsis. Reduced TM expression on endothelial cells due to inflammatory mediators, such as TNF-α, has been claimed to explain the decreased activated protein C activity. Indeed, expression of TM by the endothelium in purpuric lesions of children with meningococcal sepsis is decreased as compared with expression in control subjects.

Insufficient modulation of thrombin activity by TM and the resulting decreased inactivation of factor VIIIa and factor Va contribute to a severe procoagulant state, which promotes fibrin deposition in the microvasculature.

Thus, together these studies suggest that the reduced activation of protein C in sepsis is due to decreased availability of TM and point to the crucial anticoagulant role of the activated protein C system in the microvasculature. However, this concept is challenged by the observation that infusion of native, plasma-derived protein C in children with severe meningococcal sepsis resulted in the formation of activated protein C in vivo, and in a decrease of D-dimer levels similarly as observed on infusion of recombinant activated protein C in adult patients with sepsis [12, 14, 15].

Sepsis is a clear risk factor for thrombocytopenia in critically ill patients and its severity correlates with the decrease in platelet count. The main factors contributing to thrombocytopenia are (1) the impaired production of platelets, (2) their increased consumption in the tissues, and (3) their sequestration in the spleen. At first glance, the impaired production of platelets from the bone marrow in septic patients, despite high circulating levels of platelet-production-stimulating proinflammatory cytokines and thrombopoietin, might seem contradictory. In a substantial number of patients with sepsis, however, marked hemophagocytosis may occur [16, 17, 18]. This pathological process consists of active phagocytosis of megakaryocytes and

other hematopoietic cells by monocytes and macrophages, hypothetically in response to high levels of macrophage colony stimulating factor in sepsis. Platelet consumption probably also plays an important role in patients with sepsis. Thrombin is the most potent activator of platelets in vivo, and intravascular thrombin generation is a ubiquitous event in sepsis with or without evidence of overt disseminated intravascular coagulation (DIC). DIC frequently complicates sepsis. DIC can be found in 25–50% of patients with sepsis and seems to be a strong predictor of mortality. DIC is an acquired syndrome characterized by the activation of intravascular coagulation culminating in intravascular fibrin formation and deposition of fibrin in the microvasculature. Secondary fibrinolysis, or in later stages inhibition of fibrinolysis, accompanies coagulation activation [15, 19].

Although the initial trigger and the dynamics may differ, the clinical picture of severe sepsis or septic shock in latter stages is quite uniform. Fibrin deposition leads to a diffuse obstruction of the microvascular network resulting in progressive organ dysfunction, such as the development of renal insufficiency and acute respiratory distress syndrome, hypotension, and circulatory failure.

Then, it appears that restoration of anticoagulant capacity as well as fibrinolysis might be a promising target for therapy strategies. Since consumption of the biological inhibitors of thrombin may contribute to the formation of thrombin during sepsis, one could speculate that administration of an inhibitor of thrombin formation or a direct inhibitor of the catalytic site of thrombin might be useful in this clinical condition. However, current insights indicate that this view on the efficacy of anticoagulant proteins in sepsis is too simple. The efficacy of clotting inhibitors in sepsis models depends not only on their anticoagulant properties but also on their anti-inflammatory effects [19, 20].

6.3 Clinical Manifestations and Laboratory Investigations

The most common clinical findings in sepsis are related to SIRS (e.g., fever, tachycardia, tachypnea, and leukocytosis) and organ dysfunction (e.g., acute lung injury, acute respiratory distress syndrome, shock). Laboratory markers of the activation of the coagulation cascade are most often manifested by increased D-dimer levels (about 100% patients) and decreased levels of circulating protein C (in more than 90% of patients) [14, 17, 21].

The global coagulation tests which measure the capacity of thrombin generation, such as the prothrombin time and the activated partial thromboplastin time, show prolonged coagulation times because of the decrease of the levels of fibrinogen, prothrombin, and factors II, V, VII, IX, and X as a consequence of consumption and plasmin-induced proteolysis of these factors. Also the reduced platelet count is regarded as an indication for the dysfunction of the hemostatic system. Measurement of antithrombin activity is considered another screening test in patients since its value markedly decline over time owing to consumption [20, 22–24].

6.4 Therapeutic Approach

Based on the pathophysiologic concepts and the striking anticoagulant and anti-inflammatory properties of coagulation inhibitors in models for severe sepsis, administration of these inhibitors has been considered an attractive therapeutic approach for human sepsis. However, despite the sound physiological principles and the indications deriving from preliminary clinical studies, the results of larger trials using these substances have been largely below the expectations, with the exception of recombinant activated human protein C (drotrecogin-α, rh-PAC), which combines anticoagulant and anti-inflammatory properties [25–38]. In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, the administration of this substance was associated with a significant improvement of survival in septic patients (absolute mortality reduction, – 6.1%; relative risk reduction, 19.4%) [29]. Results were so striking that the trial was suspended earlier than expected after the second interim analysis of 1,520 patients, the trial was stopped earlier than expected. Immediately ther after, drotrecogin-alpha was released worldwide, becoming the first drug specifically marketed for the treatment of sepsis.

However, as subsequent trials failed to confirm these initial results and some investigators claimed that the anticipated end of the PROWESS trial constituted an unacceptable bias [30], another large, double-blind, controlled international trial was then launched (PROWESS-SHOCK) in which the administration of the rh-APC was restricted to patients with severe sepsis or septic shock, who were demonstrated to take more advantage from this substance than less sick patients [29, 31]. Since the yet unpublished did not demonstrate any survival difference between treated patients and controls, on October 26, 2011, the manufacturer withdrew the rh-APC from the market, and this substance is no longer available.

6.5 Conclusions

On the basis of many experimental and clinical evidences, one can conclude that inflammation and blood coagulation are intrinsically linked and that sepsis and sepsis-related conditions are associated with the simultaneous activation of both pathways. Despite a number of trials involving several different molecules, the only substance with anticoagulant properties which has been demonstrated to reduce mortality in patients with severe sepsis and septic is drotrecogin-α. However, as confirmatory trials did not confirm the initial beneficial effects on the outcome, recently this substance has been withdrawn.

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