Anticoagulation in severe sepsis and the multiple organ dysfunction syndrome

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Chapter 1

General introduction and outline of the thesis
Introduction

Patients with severe sepsis and the multiple organ dysfunction syndrome (MODS) represent continuing challenges in modern critical care medicine, due to their significant number and high mortality rate. In the United States, the annual incidence of sepsis is approximately 750,000, with an associated mortality rate of 30% [1]. Sepsis is defined as severe when it is accompanied by acute organ dysfunction [2]. In the Netherlands, severe sepsis carries an annual intensive care unit (ICU) admission rate of approximately 8500 (11% of all ICU admissions) [3], with a mortality rate of 38% [4]. MODS is a syndrome which emerged when the care for the critically ill patient improved enough to keep such patients alive. MODS occurred in the United States in the 1980s in 14% of all ICU admissions, with a mortality rate of over 50% [5].

MODS occurs as a consequence of failing tissue perfusion and therefore can have multiple causes. In a survey of 2475 patients with MODS, nonoperative diagnoses accounted for three quarters of the admissions, with five primary conditions accounting for almost half of the nonoperative MODS admissions: cardiac arrest, sepsis, pneumonia, congestive heart failure and upper gastrointestinal bleeding [5]. MODS can include the failure of six organ systems: the cardiovascular, respiratory, hepatic, renal, hematologic and neurologic system. Acute failure of the renal system carries the worst prognosis: the mortality of critically ill patients requiring renal replacement therapy varies from 60 to 80% [6-8].

In the pathogenesis of both sepsis and MODS, coagulation plays an important role. During sepsis, the coagulation system is initiated by inflammatory mediators such as endotoxin and cytokines, which are able to induce tissue factor expression on monocytes and macrophages [9]. MODS is initiated by microvascular thrombosis, impairing the blood supply to various organs [10,11]. In view of the role of coagulation in the pathogenesis of both sepsis and MODS, anticoagulant treatment of these patients has gained a renewed interest in recent years. In sepsis, anticoagulant therapy has focused on different strategies to inhibit thrombin generation. In MODS, antithrombotic strategies are mainly used to support continuous renal replacement therapy for acute renal failure.
Anticoagulation in endotoxemia and sepsis

During sepsis, thrombin generation and fibrinogen conversion are enhanced, facilitating intravascular coagulation. Coagulation is initiated by inflammatory mediators such as endotoxin and cytokines, inducing tissue factor expression [9]. Formation of the tissue factor-factor VIIa complex (TF/FVIIa) generates factor Xa, which complexes with factor Va to convert prothrombin to thrombin [12]. As thrombin is the most potent agonist of platelet activation, it promotes platelet adhesion and aggregation, thus further contributing to thrombus formation. In addition to its role in clot formation, thrombin has many pro-inflammatory properties, including the promotion of leukocyte chemotaxis, activation and rolling [10]. Under physiological conditions, thrombin activity is for an important part regulated by the protein C system. Binding of thrombin to thrombomodulin increases the rate of protein C activation approximately 1000-fold [10]. Moreover, the activation of protein C by the thrombin-thrombomodulin complex is augmented again five-fold by the binding of protein C to the endothelial protein C receptor (EPCR) [11]. Once activated protein C (APC) is generated, it binds to protein S and this complex then inactivates factors Va and VIIIa, thus further inhibiting thrombin generation [10]. During sepsis however, the expression of thrombomodulin and EPCR is downregulated, leading to inadequate activation of protein C and therefore to inadequate inhibition of thrombin generation.

Considering the central role of thrombin in both coagulation and inflammation during sepsis, novel modalities for the treatment of sepsis have been aiming at the inhibition of thrombin generation. This can be achieved at different levels: First, the TF/FVIIa complex can be inhibited, as it plays a major role in the initiation of thrombin generation during sepsis. Second, thrombin activity or generation can be limited by the administration of natural anticoagulants such as antithrombin or APC. During the last 5 years, the results of three large trials evaluating the inhibition of thrombin activity or generation during sepsis have been published. The OPTIMIST trial studied the effects of the administration of recombinant tissue factor pathway inhibitor (rTFPI) in severe sepsis [13]. Although rTFPI significantly inhibited thrombin generation in vivo, there was no difference in all cause mortality between the rTFPI and control groups. Furthermore, the KyberSept trial demonstrated that treatment of severely septic patients with high-doses of antithrombin (AT) did not improve mortality either [14]. However, the PROWESS study demonstrated that treatment of severely septic patients with recombinant human APC (rhAPC) was associated with a reduction in the relative risk of death of 19.4% [1]. As these three agents all inhibit thrombin generation, it is not clear why mortality reduction was only achieved by treatment with rhAPC and not by the administration of rTFPI or AT. Several questions arose: First, is rTFPI potent enough to limit the proinflammatory properties of thrombin? Second, does rhAPC have other properties that rTFPI and AT are lacking?
Third, are there other factors which could influence the stimulation of thrombin generation during sepsis? The present thesis tries to contribute to the elucidation of these unanswered questions.

**Anticoagulation in continuous renal replacement therapy**

In the management of critically ill patients requiring continuous renal replacement therapy, continuous venovenous hemofiltration (CVVH) is increasingly used. During this procedure, thrombosis in the extracorporeal circuit is a frequently encountered problem. Several studies have addressed its pathophysiology, but the exact mechanism by which it occurs, has not yet been elucidated. Multiple factors may play a role: the extracorporeal circuit itself, treatment modalities, platelets, coagulation factors, natural anticoagulants and fibrinolysis [15,16]. In order to select the most appropriate anticoagulant in each patient needing CVVH, knowledge of the pathophysiology of coagulation in the extracorporeal circuit is required.

The importance of the baseline platelet count in the initiation of thrombosis in the extracorporeal circuit has been debated. The group of Salmon and Cardigan found no correlation between baseline platelet count and circuit survival time [17,18], whereas other investigators demonstrated that patients with higher initial platelet counts required more heparin to reach the same circuit survival time [19,20]. In addition, the finding that the use of platelet aggregation inhibitors such as prostacyclin improved circuit survival time [21], underscores the role of platelets in the initiation of coagulation in the extracorporeal circuit.

The role of the coagulation system has been studied extensively. Salmon et al. demonstrated the lack of influence of hemofiltration on the intrinsic coagulation pathway [17]. However, the tissue factor pathway seems to play an important role in the initiation of coagulation in the extracorporeal circuit. Expression of tissue factor on circulating and adherent monocytes has been demonstrated in an *in vitro* model of extracorporeal circulation [22]. Cardigan and colleagues demonstrated an increase in tissue factor during hemofiltration, associated with thrombin generation and inversely correlated with circuit survival time [18].

As levels of natural anticoagulants can be depressed in critically ill patients, this may play a role in the initiation of coagulation in the extracorporeal circuit. Premature clotting of the hemofilter has been associated with low baseline levels of antithrombin [17]. Schrader *et al.* reported improved circuit survival times after antithrombin suppletion in patients with antithrombin deficiency [23]. Although protein C levels are known to be depressed in the critically ill, there is no evidence that low levels of protein C contribute to premature hemofilter clotting.
Chapter 1

Since uremia is associated with a fall in fibrinolytic capacity [24], and critical illness can be associated with increased levels of plasminogen activator inhibitor type 1 (PAI-1), it is conceivable that impaired fibrinolysis also contributes to the pathogenesis of thrombosis in the extracorporeal circuit. However, this aspect has never been investigated.

Aims and outline of this thesis

The aims of this thesis were to study the pathophysiological mechanisms by which the activation of coagulation influences the outcome of sepsis and MODS, and to understand how anticoagulant therapy can contribute to a favorable outcome in this patient group. We have focused on two aspects: anticoagulation in sepsis and anticoagulation during CVVH.

The first part of this thesis addresses anticoagulation in sepsis. Three studies are presented: two studies investigating different strategies aimed at the inhibition of thrombin generation during endotoxemia and sepsis and a pathophysiological study concerning the effects of endotoxemia on the resistance to APC in healthy humans. In Chapter 2, we studied the influence of rNAPc2, a potent inhibitor of TF/FVIIa, mechanistically distinct from rTFPI, on endotoxin-induced coagulation and inflammation in healthy volunteers. In Chapter 3, we studied the extent to which APC resistance occurs in healthy humans during endotoxemia and we evaluated the mechanism by which this occurs. In Chapter 4, we studied the effect of treatment with rhAPC on parameters of coagulation and inflammation in patients with severe sepsis.

The second part of this thesis addresses anticoagulation during CVVH. Four studies and a guideline are presented. The four studies include a pathophysiological study concerning the initiation of coagulation during CVVH and three clinical studies addressing three different strategies aiming at the inhibition of coagulation in the extracorporeal circuit. In Chapter 5, we studied the pathophysiology of coagulation in the extracorporeal circuit in ten critically ill patients during CVVH without anticoagulation. In Chapter 6, we compared predilutional to postdilutional CVVH in eight critically ill patients, with respect to thrombogenesis in the extracorporeal circuit and clearance, using the low molecular weight heparin nadroparin as an anticoagulant. This study was performed as a prospectively randomized cross-over study. In Chapter 7, we compared the use of two different low molecular heparins during CVVH in a prospectively randomized cross-over study. In Chapter 8, we compared the use of rhAPC and heparin as anticoagulants during CVVH in three critically ill patients with severe sepsis. In Chapter 9, we formulated guidelines for the use of unfractionated heparin and low molecular weight heparins as anticoagulants during CVVH. The results of our studies are summarized in Chapter 10.
Introduction

References


