The extrinsic coagulation pathway in coronary artery disease and endotoxemia
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Summary

This thesis focuses on the activation and inhibition of the extrinsic coagulation pathway in ischemic coronary disease, during coronary percutaneous intervention, and in experimental endotoxemia.

From the overview in chapter 2, it appears that the enhanced expression of TF may play a significant pathogenic role in patients with (coronary) atherosclerosis and in the subgroup that is treated with percutaneous coronary interventions. Increased expression of TF antigen and activity by circulating monocytes and by different cell-types in human atherosclerotic plaques may initiate thrombotic complications. This hypothesis is supported by experimental studies in animals demonstrating reduced thrombus and neointima formation at the site of vascular injury after inhibition of the extrinsic coagulation pathway.

The triage of patients presenting with chest pain to the emergency department (ED) is a challenge for physicians, especially in cases with an initial non-diagnostic electrocardiogram (ECG). As thrombus formation after coronary plaque disruption plays a major role in patients with an acute coronary syndrome (ACS), we studied this in chapter 3 the diagnostic utility of coagulation and fibrinolytic markers, which may predominantly useful especially in ACS cases without evidence of myocardial injury. Compared to control subjects, plasma levels of thrombin generation markers, soluble TF and tissue factor pathway inhibitor (TFPI) activity were not increased in cases with (cardiac troponin T (cTnT) positive or negative) ACS, whereas levels of plasminogen activator inhibitor (PAI) were enhanced in the ACS cases, which reached statistical significance for the subgroup of cases with cTnT negative ACS. The positive (PPV) and negative (NPV) predictive values to detect ACS cases by these markers varied between 68% and 75% and between 40% and 43%, respectively. To detect the subgroup with cTnT negative ACS, only TFPI and PAI showed diagnostic utility. However, the PPVs were low at 43% and 55%, respectively. Thus, although plaque disruption with thrombus formation is the most common underlying pathogenic mechanism during an ACS, in this patient population in whom additional markers of ACS are highly needed, this does not lead to diagnostic elevation of systemic plasma levels of coagulation and fibrinolytic markers.

Chapter 4 reports the first study of TF/factorVIIa inhibition by rNAPc2 in patients with coronary artery disease who underwent elective percutaneous coronary
intervention (PCI). The main objective of this randomized, placebo-controlled trial was to evaluate the safety of escalating doses of rNAPc2 on top of standard treatment during PCI. A secondary objective was to investigate the ability of the rNAPc2 dosages to inhibit thrombin generation during and after the intervention. Compared to placebo treated patients, the incidence of minor bleeding episodes did not increase at the lowest three rNAPc2 doses, whereas a significant increase was observed at the highest dose group of 10.0 µg/kg. Three of a total of four patients that experienced a major bleeding had received a glycoprotein IIb/IIIa receptor antagonist in addition to rNAPc2 at the moment of the bleeding. Regarding the secondary objective, all rNAPc2 dose groups demonstrated significant suppression of thrombin generation compared to the placebo group. These results suggest that inhibition of the TF/factor VIIa complex with rNAPc2, at doses up to 7.5 µg/kg, in combination with aspirin, clopidogrel, and unfractionated heparin appears to be a safe and effective strategy to suppress thrombin generation during coronary angioplasty. Additional research is warranted evaluating the safety of the concomitant use of rNAPc2 and a glycoprotein IIb/IIIa receptor antagonist. In chapter 5, we present in detail the findings on coagulation and inflammation in those patients that underwent intracoronary stenting. In contrast to the increased inflammatory response, coagulation activation after coronary stent implantation that is observed in spite of the use of multiple antithrombotic drugs, can be attenuated by inhibition of the extrinsic coagulation pathway using rNAPc2. We hypothesize that the inhibition of the TF mediated pathway of coagulation activation may be an important target to prevent thrombotic complications after coronary stenting. Taken together, the results presented in chapter 4 and 5 support further investigation of the safety and efficacy of rNAPc2 in patients with acute coronary syndromes.

In chapter 6 we investigate the ability of recombinant factor VIIa (rFVIIa), an activator of the extrinsic coagulation pathway, to antagonize the anticoagulant effects of the pentasaccharide fondaparinux in healthy male volunteers. Recombinant FVIIa was previously demonstrated to restore thrombin generation during inhibition of the TF/factor VIIa complex by rNAPc2. The current study showed that rFVIIa also reversed the inhibitory effects of fondaparinux on thrombin generation and on coagulation times, with a duration of 2 to 6 hours. Based on these findings, we postulate that rFVIIa may be a suitable antidote in case of serious bleeding complications in patients treated with fondaparinux.
In chapter 7 and chapter 8 we describe the effects of rNAPc2 administration on coagulation and inflammation during experimental endotoxemia in chimpanzees and human volunteers, respectively. Both studies showed that rNAPc2 completely blocked the endotoxin induced thrombin generation, while the activation and subsequent inhibition of the fibrinolytic mechanism after endotoxin infusion was not affected by rNAPc2. In chimpanzees we also observed a significant reduction of factor X activation peptide plasma levels and no effect on levels of factor IX activation peptide after rNAPc2 administration. These results suggest that the intrinsic route in the activation of the coagulation system appears less important in this model of endotoxemia, and that the pivotal role of the extrinsic coagulation pathway in endotoxin induced coagulation activation is confirmed by these studies. The inflammatory response was studied in the human subjects, we found that rNAPc2 does not affect this response, except for an attenuation of the endotoxin-induced increase of interleukin (IL) 10 plasma levels. The interplay between the TF/factor VIIa complex and IL-10 is largely unknown. Therefore, the role of IL-10 suppression by rNAPc2 needs to be explored in human endotoxemia and sepsis. Thus, although rNAPc2 may be a promising therapeutic option to inhibit coagulation activation in patients with sepsis, its effects on morbidity and mortality remain to be elucidated.

In chapter 8 we also examined in a separate group of male human volunteers the pharmacokinetics and pharmacodynamics of escalating rNAPc2 doses after a single intravenous administration, which was performed for the first time in humans. It resulted in a dose-dependent reduction of the endogenous thrombin potential, a measure of the residual ability of thrombin generation in plasma after the administration of rNAPc2. It also resulted in a biological half-life of more than 50 hours and in a dose-dependent prolongation of the prothrombin time, which was comparable to the observations after a single subcutaneous administration of rNAPc2. This is important information that may serve as a basis for future studies on the effects of rNAPc2 in patients with acute coronary syndromes, and who will receive this drug by an intravenous administration.

In summary, new antithrombotic drugs allow specific interventions in the coagulation cascade with great precision. This does not only expend our therapeutic potential, the findings of investigations such as ours also add to the knowledge of the underlying biology of arterial (athero)thrombotic diseases.