Infections, coagulation and thrombosis
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General introduction and outline of the thesis

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Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), have an annual incidence of approximately 2–3 per 1000 people [1]. Many risk factors of VTE have been well established, including genetic predisposition, immobilization, surgery, pregnancy, oral contraceptives and malignancies. However, there are patients who develop VTE in the absence of one of these risk factors.

Arterial cardiovascular disease (CVD) leads to approximately 10 million deaths per year worldwide, including coronary artery disease and stroke [2]. Risk factors include genetic predisposition, smoking, obesity, hypertension and diabetes. Both VTE and CVD lead to important morbidity and mortality. As is the case with VTE, there are unknown risk factors for developing CVD.

There is direct and indirect evidence that acute as well as chronic infections are associated with an increased risk of developing VTE and CVD, and may form an independent risk factor for developing VTE and CVD. For example, atherosclerosis is considered to be an inflammatory disease [3]. It has been shown that systemic inflammation and infections accelerate atherogenesis in animals [4]. Inflammation does not only play a role in early atherogenesis, but also may be an important factor in the development of acute coronary artery disease [5]. Studies have shown that there is an association between the incidence of atherosclerosis and the presence of for example herpes virus and cytomegalovirus (CMV) [6,7], and that inflammatory markers predict the outcome in acute vascular events [8,9]. Furthermore, an increasing body of evidence suggests an extensive cross-talk between inflammation and coagulation. Inflammation leads not only to activation of coagulation, but coagulation also considerably affects inflammatory activity [10,11]. Inflammation has an impact on initiation, propagation and the inhibitory phases of blood coagulation [12]. An example of activation of coagulation through inflammatory mediators was shown in a population-based case-control study, where subjects with elevated IL-8 levels had an increased risk of venous thrombosis, which indicates the role of inflammation (potentially as a consequence of infection) in the pathogenesis of venous thrombosis [13].

Activation of the coagulation system has been described in bacterial infections, viral infections, protozoa (malaria) and fungi [14]. Besides several pathogens, also inflammatory cells and mediators can induce the expression of tissue factor (TF), which is the major activator of coagulation, on monocytes and on endothelial cell surfaces. In addition, inflammatory cells and mediators downregulate natural anticoagulant proteins (such as protein C and antithrombin) and fibrinolysis (the process of lysis of the blood clot), with consequent intravascular deposition of fibrin. It is further known that inflammation leads to downregulation of thrombomodulin and the endothelial cell protein C receptor (EPCR) via different cytokines, thereby reducing the ability to generate the natural anticoagulant activated protein C (APC) [15], and to inhibition of fibrinolysis by elevated levels of plasminogen activator inhibitor 1 (PAI-1) [16]. Coagulation activation and dysfunctional physiological anticoagulant pathways, most notably the protein C system, are the hallmarks of the inflammation-induced prothrombotic state [17]. Inflammation can also increase the number of platelets via inflammatory mediators like interleukin 6 and these newly formed platelets appear to be more thrombogenic [11]. Direct or indirect activation of the endothelium
by bacteria, viruses or other pathogens may thus result in altered coagulation and fibrinolytic systems [14], leading to an imbalance between coagulation and natural anticoagulation. A balance between these two states is part of the host defense against infectious agents.

Endothelial cell perturbation and coagulation activation are associated with an increased risk of future ischaemic heart disease. Von Willebrand factor (VWF), a marker of endothelial cell perturbation, mediates platelet adhesion and plays a role in thrombus formation. High VWF levels are also related to a short-term increased risk of plaque rupture and subsequent thrombus formation [18]. In addition, increased levels of other haemostatic markers, such as prothrombin fragment 1+2, PAP, resistance to activated protein C (APC), increased thrombin generation and PAI-1, are risk factors for ischaemic heart disease [19-23].

From the 1960’s until present, increased mortality and hospitalizations due to cardiovascular and cerebrovascular causes have been observed during influenza epidemics [24,25]. In a case-control study, in which patients with an acute myocardial infarction and matched controls were compared, there was a statistically highly significant association of symptoms of respiratory tract infection with the onset of myocardial infarction [26]. Recently, acute respiratory tract infections have been associated with a temporary increase of the risk of acute ischaemic heart disease and stroke [27,28]. The first three days after the clinical diagnosis of an acute respiratory infection has been made, there is a 5-fold increased risk of developing a myocardial infarction in elderly people. In addition, it was also found that there was an association between respiratory tract infections and a first episode of acute myocardial infarction for a period of 10 days [29]. If respiratory tract infections and especially influenza are related to acute coronary syndromes, it is conceivable that vaccination against influenza may protect against cardiovascular complications. Indeed, studies have shown a protective effect of vaccination against influenza on hospitalization for (recurrent) coronary heart disease and cerebrovascular disease, as well as future myocardial infarction or ischaemic stroke [30-32]. However, results are not uniform [27,33].

Besides the association between respiratory tract infections and CVD, it has been observed that signs of respiratory tract infection are associated with an increased risk of VTE [34]. The risk of venous thrombotic disease is increased 2-fold in the first two weeks after a respiratory tract infection, gradually falling over the subsequent months. The precise underlying mechanism of the association between respiratory tract infections and VTE and CVD is unclear, but systemic inflammation upon infection may be one of the contributing mechanisms [35,36]. Infection-induced systemic inflammation with transient change in local hemodynamic factors, transient coagulation activation and endothelial cell perturbation may contribute to this [6,37]. Whether this is true in respiratory tract infections caused by viruses and to what extent remains uncertain.

In vitro studies showed that monocytes and endothelial cells that were incubated with influenza virus are able to activate coagulation, causing a reduction in clotting time and a 4- to 5-fold increase in the expression of tissue factor [38,39]. Furthermore, it has been demonstrated that respiratory viruses are able to increase thrombin generation by reduced levels of protein C [40]. There are also indications that influenza leads to a procoagulant state of the blood in vivo. Several cross-sectional reports showed increased levels of haemostatic proteins (such as
fibrinogen) and decreased levels of natural anticoagulants (such as proteins C and S) during symptoms of acute respiratory tract infection [41-43]. However, these findings are difficult to interpret, since the diagnosis of respiratory tract infection was not unequivocally established. Whether viruses infecting the respiratory tract indeed perturb endothelial cells and thereby increase the risk of acute ischaemic heart disease remains to be proven.

The aim of this thesis was to further investigate whether viral infections, and in particular acute respiratory tract infections and CMV, are associated with an increased risk of VTE and CVD. We hypothesized that one of the possible mechanisms behind this association was activation of coagulation, resulting in a higher risk of venous thrombosis and ischaemic heart disease. The importance of understanding the pathophysiological mechanisms of changes in coagulation during respiratory tract infections is important for developing preventive and treatment strategies. The recent outbreak of Swine flu, also known as Mexican flu (H1N1), showed that vascular complications are an important feature of the disease and leads to high morbidity and mortality [44,45], and this underlines the importance of knowledge of disease pathophysiology. Understanding of the influenza-induced prothrombotic state might improve prevention of venous thrombotic disease and ischaemic heart disease during influenza epidemics.
This thesis describes the association between viral infections and venous thrombosis and cardiovascular disease, in particular viruses that cause respiratory tract infections. We hypothesized that one of the possible mechanisms behind this association was activation of coagulation. We investigated the underlying pathogenesis of 1) the epidemiological observation that the incidence of myocardial infarction is increased during the influenza season; 2) the observed association between respiratory tract infections and VTE. 

**Chapter 2** reviews the association between different viruses, both hemorrhagic viruses and non-hemorrhagic viruses, both acute and chronic viral infections, and virus-induced changes in coagulation as well as related clinical pictures. 

**Chapters 3 and 4** concern the effect of naturally occurring respiratory tract viral infections on coagulation in cohorts of human subjects of 55 years of age and older, selected from a population of a General Practitioners office. 

**Chapter 5** describes the effect of influenza infection in mice on coagulation and the effect of administration of reconstituted High Density Lipoprotein (rHDL) immediately after infection. Since HDL has anti-inflammatory properties, we hypothesized that the influenza induced activation of coagulation would be attenuated by administration of rHDL. 

In **Chapter 6** we studied the association between respiratory tract infection and pulmonary embolism in a cohort of patients presenting with a clinical suspicion of having pulmonary embolism. 

In **Chapter 7** we studied the presence of respiratory tract infections in patients admitted to the Coronary Care Unit with an acute coronary syndrome to study the association between viral respiratory infections and cardiovascular disease. 

**Chapter 8** concerns a study of renal transplant patients with (reactivation of) cytomegalovirus (CMV) infection and the effect of this infection on coagulation. 

In **Chapter 9** we report two cases of Lemierre’s syndrome, a bacterial infection of the head and neck region with thrombosis of the internal jugular vein. It also contains a review of Lemierre’s syndrome. This chapter is a clinical example of the relationship between infection and venous thrombosis and its complications.
REFERENCES