Asthma and coagulation: A clinical and pathophysiological evaluation

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Chapter 1

General introduction
Asthma

Asthma is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, chest tightness and coughing\(^1\). Airway inflammation in asthma can be induced by environmental agents, including inhaled allergens, occupational agents and viruses in genetically predisposed individuals. The estimated prevalence of asthma is between 1-18% worldwide depending on the region. In The Netherlands, the total number of asthmatic patients has been estimated to be 578,000 in the year 2011, a prevalence of around 34 per 1000 inhabitants\(^2\). Although asthma can be well controlled with inhalational corticosteroid (ICS) treatment in most patients, there is still a subset of patients with severe asthma requiring chronic oral corticosteroids for control of their disease. The prevalence of severe refractory asthma, defined as asthma that remains uncontrolled despite treatment with high doses of inhaled corticosteroids and longacting β2-agonists, is ≈3.6% of the total asthma population in The Netherlands\(^3\).

Pathophysiology of asthma

Inflammation of the airways is a consistent and characteristic feature of asthma that is strongly associated with airway hyperresponsiveness and asthma symptoms\(^1\). It involves several inflammatory cells and multiple mediators resulting in characteristic pathophysiological changes\(^4\). The characteristic pattern of inflammation in asthma involves activated mast cells, increased numbers of activated eosinophils and increased numbers of natural killer and T-helper cells, which release mediators and contribute to symptoms. Structural cells of the airways, including epithelial cells, smooth muscle cells, endothelial cells, fibroblasts and myofibroblasts, also produce inflammatory mediators and contribute to the persistence of inflammation in various ways\(^1,4\). Induced sputum has been a particularly valuable research tool for examining airway inflammation in asthma\(^5\). Normal sputum barely contains eosinophils, but in untreated patients with symptomatic asthma increased eosinophil counts are typical. In patients with severe asthma, sputum eosinophils may even persist despite treatment with high doses of inhaled or oral corticosteroids. These patients with persistent airway eosinophilia are particularly at risk of frequent severe asthma exacerbations\(^6\) and accelerated decline in lung function\(^7\).
Inflammation and coagulation

Inflammation and coagulation are not just interdependent but highly integrated systems\(^8\),\(^9\). Inflammation often leads to activation of coagulation. Inflammation has evolved to remove pathogens, harmful cells and materials from the body. But inflammation comes at the cost of local tissue injury. Tissue injury results among others in endothelial damage with plasma leakage in the extracellular tissue as a consequence. Upon endothelial damage tissue factor (TF) is released and initiates together with factor VII the extrinsic coagulation cascade (Figure 1). As a result of activation of hemostasis, blood clots are formed by fibrin and activated platelets.

**Figure 1.**
Extrinsic coagulation cascade and fibrinolytic system

These blood clots prevent blood loss from the tissue-damaged areas.

Hemostasis has another role beside the prevention of blood loss. It also prevents spreading of pathogens to other tissues\(^10\). In the formation of blood clots neutrophils and monocytes are entrapped. These neutrophils and monocytes are recruited to these clot formations by signals depending on the trigger and subsequently activated. Neutrophils are activated to form neutrophil endothelial traps (NETs).

NETs are comprised of a matrix of DNA and histones catapulted out of neutrophils upon activation by for example pathogen-associated molecular patterns\(^10\).
not only kill the pathogens inside the blood clots, they also activate the intrinsic pathway by activating factor XII. Furthermore, NETs bind to von Willebrand factor and thereby activate platelets through the released histones. Finally, NETs inactivate anticoagulant proteins like tissue factor pathway inhibitor and thrombomodulin by the release of enzymes like elastase and myeloperoxidase. This suggests that coagulation plays an important role in the host defence against invading pathogens.

The close interaction between coagulation and inflammation implies that these systems need to be well controlled as a disbalance in one of the two systems may have an effect on the other system.

Therefore the hemostatic balance is maintained by the fibrinolytic system and the natural anticoagulants, such as antithrombin, tissue factor pathway inhibitor, and the protein C system. The inflammatory balance is maintained by pro- and anti-inflammatory cytokines. If these control mechanisms fail, complications may occur. For example, a failure in coagulation may lead to lethal disseminated infections and autoimmune inflammatory diseases may lead to activation of coagulation resulting in venous thrombosis. Interference in one of the two systems may have an effect on the other system. The anticoagulant dabigatran, a direct thrombin inhibitor, reduces fibrotic changes in mice with an interstitial lung disease, whereas corticosteroid treatment may induce venous thrombosis.

**Corticosteroids and coagulation**

As early as the 1950s adrenocorticotropic hormone and corticosteroids were thought to be associated with activation of the hemostatic system. Several studies suggested that corticosteroids are procoagulant. In patients with Cushing’s disease or in patients on maintenance corticosteroid therapy, coagulation is activated, leading to a modest prothrombotic effect. The effect of glucocorticosteroids on pro-, anticoagulant and fibrinolytic factors may diverge, depending on the situation in which they are prescribed (in healthy subjects or patients with active disease). In patients with a renal transplant for instance, long-term oral corticosteroid treatment leads to a procoagulant state by an increase in PAI-1. After discontinuation of corticosteroid treatment, PAI-1 levels dropped dramatically. However, in a prospective study in healthy individuals, oral dexamethasone 3 mg twice daily for 5 days modestly increased clotting factors VII, VIII and IX, without affecting PAI-1, D-dimer or soluble CD-40 ligand. In this study, thrombin-antithrombin complexes (TATc) and prothrombin fragment 1+2 were not measured.
Asthma and coagulation

Hemostasis may also be activated in asthma, probably as a result of inflammation\textsuperscript{21-24}. In induced sputum, Thrombin, TF and TATc levels are increased in asthmatic mice and humans\textsuperscript{23,25,26}. Thrombin and TF are correlated with eosinophil count and with eosinophilic cationic protein in induced sputum\textsuperscript{23,25}. Thrombin and TATc are also correlated with airway hypersensitivity in patients with asthma\textsuperscript{25}. In a murine asthma model activated protein C (APC) is reduced and supplementation of APC is shown to reduce the immunologic and inflammatory Th-2 response\textsuperscript{26}. None of these studies examined if the activation of coagulation results in clinical symptoms. The clinical consequence of hemostatic activation may be an increased risk of pulmonary embolism, especially when exacerbations of asthma occur. Asthma disease exacerbations are caused among others by allergens, viral infections (like rhinovirus or RS-virus) or compliance to inhaled and/or oral corticosteroid therapy. The effect of allergen induced asthma exacerbations on coagulation has previously been studied, and showed an increased in procoagulant markers in bronchoalveolar fluid\textsuperscript{22}. Whether more specific disease exacerbations in asthma (like rhinovirus and compliance to therapy) also induce a procoagulant response is unknown.

Scope of the thesis

Hemostasis is activated in the airways of patients with asthma after an allergic challenge. It is unknown if local activation of coagulation in the airways due to respiratory viral infections, such as the common rhinovirus, leads to activation of coagulation, and whether this activation may induce venous thromboembolism. Second, corticosteroid therapy may also be procoagulant, but this effect has not been thoroughly studied, nor has the potential association with the risk of thrombosis.

If asthma exacerbations or its treatment increase the risk of venous thromboembolism, thromboprophylactic treatment may be important in these circumstances. However, anticoagulant treatment increases the risk of bleeding, so as a first step, a better insight in the clinical and pathophysiological effects of viral infections and corticosteroid treatment in patients with asthma are mandatory.
Aims of the thesis

The aims of this thesis are:
1. To investigate the interaction between asthma and coagulation in general, on disease severity and clinical implication as specified by the occurrence of venous thromboembolism.
2. To investigate the interaction between corticosteroid treatment and coagulation in patients with asthma and healthy controls and the clinical implication specified by the occurrence of pulmonary embolism in patients using oral corticosteroids.
3. To investigate the effect of rhinovirus infection on coagulation in patients with asthma and healthy controls.

Outline of the thesis

In Part I of this thesis the interaction between coagulation and asthma is being presented in three chapters. The current knowledge on the subject of asthma and coagulation is discussed in a narrative review presented in chapter 2. The association between asthma and pulmonary embolism and venous thrombosis, investigated in a cohort of 648 patients collected in three Dutch asthma clinics, is described in chapter 3. In chapter 4, we investigated the influence of asthma severity on coagulation in 93 patients with asthma and 33 healthy control subjects in a cross-sectional analysis.

Oral corticosteroids are the mainstay of treatment of asthma exacerbations and the maintenance treatment in patients with severe asthma. Therefore, Part II of this thesis describes the role of oral corticosteroids on coagulation. In chapter 5, the association between type and duration of corticosteroid therapy, and the incidence of a first pulmonary embolism is investigated using the PHARMO database cohort. In chapters 6 and 7, the effect of a 10-day 0.5mg/kg/day oral prednisolone course on coagulation is investigated in a double blind randomised placebo-controlled study in patients with asthma of different severity and healthy subjects.

Finally in Part III we investigated the effect of asthma exacerbation on coagulation in an in vivo human rhinovirus model in patients with mild asthma and healthy control subjects (chapter 8).

To conclude, in chapter 9 the results of this thesis are summarized, discussed and implications for future research are suggested.
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