Risks of thrombophilia and diagnostics of pulmonary embolism

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Chapter 1

Introduction

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Risks of thrombophilia

Deep venous thrombosis and pulmonary embolism are diseases that have been recognised by physicians as far back as the Middle Ages. However, the linkage between the two diseases was first suggested only in 1856 by the German pathologist Virchow, who hypothesised that pulmonary emboli may originate from the deep veins of the leg.[1] Heavily criticised in his own time, the medical community eventually, although only relatively recently, accepted Virchow's hypothesis. A number of studies have shown that the majority of patients with symptomatic deep vein thrombosis of the leg have accompanying asymptomatic pulmonary emboli, and vice versa. Based on these studies, deep vein thrombosis and pulmonary embolism are currently considered to be one clinical entity - venous thromboembolism.

The etiology of venous thromboembolism has been a topic of much research in the past fifty years. Attention was initially primarily focussed on clinical conditions that were shown to be associated with an increased risk for venous thromboembolism, such as surgery, trauma, immobilisation, and pregnancy. More recently, however, haemostatic alterations leading to a disturbance in the balance between fibrin formation and degradation have been under investigation as a cause of venous thromboembolism.

In 1965 Egeberg first described an inherited deficiency of antithrombin, a physiological inhibitor of coagulation, leading to a tendency towards venous thrombosis in a Norwegian family.[2] He coined the term 'thrombophilia' to describe this increased risk for venous thromboembolism. The discovery of this first hereditary risk factor was quickly followed by the description of heritable deficiencies of protein C and protein S. These two proteins are part of another physiological system that downregulates thrombin formation. These three deficiencies together were found to be present in approximately 5-10% of consecutive patients with documented venous thromboembolism. After a period of relative silence in this research area, the past five years have been filled with discoveries of new thrombophilic risk factors, such as the Factor V Leiden mutation leading to activated protein C resistance, the prothrombin mutation associated with an increased level of Factor II, increased levels of Factor VIII, and hyperhomocysteinemia. At present a thrombophilic risk factor can be found as a causative factor in approximately 60-70% of unselected patients with venous thromboembolism.

There is a large amount of data concerning the relative risk for venous thromboembolism in patients with these various thrombophilic abnormalities as compared with the normal population. However, it remains largely unknown what the true incidence of venous thromboembolism, both spontaneous and risk period-related (surgery, trauma, immobilisation or pregnancy),

is in these patients. This information is essential for adequate counselling of, and therapeutic management decisions in, patients with thrombophilic abnormalities.
Another unresolved issue is the risk of complications, other than venous thromboembolism, associated with these defects. The association between an acquired thrombogenic disorder, lupus anticoagulant, and an increased risk for poor pregnancy outcome has been well documented. It has been hypothesised that this is caused by fibrin formation in the placental vessels, leading to infarction and placental insufficiency. Whether the heritable thrombophilic risk factors are also associated with such an increased risk for fetal loss remains unknown. Knowledge of such an association is of clinical importance, as it may have therapeutic consequences.

Outline thesis part one

The first part of this thesis entitled 'Risks of thrombophilia' addresses some of the issues mentioned above. In **Chapter 2** the incidence of venous thromboembolism, both spontaneous and related to risk periods, was evaluated in a large retrospective study of families with a deficiency of antithrombin, protein C, or protein S or with the Factor V Leiden mutation. The relatively low incidence that was found in this investigation was confirmed in a prospective cohort study in asymptomatic subjects with a deficiency of antithrombin, protein C or protein S, of which the results are described in **Chapter 3**. The risk for recurrent venous thromboembolic complications in patients with these deficiencies, of importance for decisions regarding the duration of anticoagulant therapy, was investigated in **Chapter 4**.
In **Chapter 5** the risk for venous thromboembolism in female carriers of an antithrombin, protein C or protein S defect during pregnancy and the postpartum period is investigated and the implications for anticoagulant prophylaxis are discussed. **Chapter 6** examines the hypothesis of an increased risk for abortion and stillbirth in women with one of the aforementioned deficiencies. The findings in chapter 5 and chapter 6 have led to the concept that there may be a beneficial effect of prescribing anticoagulant prophylaxis in a subgroup of thrombophilic women during pregnancy and the postpartum period. **Chapter 7** describes the results of a systematic review of the safety of low-molecular-weight heparins, a new category of anticoagulant drugs, during pregnancy. In this review both the risks for the fetus (with regard to adverse outcome) as well as for the mother (with regard to complications) were evaluated. In the final chapter of the first part of this thesis, **Chapter 8**, an interim evaluation of a strategy for the optimal management, during preg-

nancy and the postpartum period, of women considered to be at an increased risk for venous thromboembolism is presented.

Diagnostics of pulmonary embolism

Although deep venous thrombosis of the lower extremity and pulmonary embolism are considered to be one clinical entity, the diagnostic approaches in patients suspected of these diseases have developed relatively independent of each other.

Since the demonstration of the lack of specificity of the clinical diagnosis of deep venous thrombosis by Haeger in 1969,[3] objective confirmation of the diagnosis has generally been considered necessary. Venography is regarded as the reference method for the diagnosis of deep venous thrombosis of the leg. However, due to its drawback as an invasive technique, the need for alternative, non-invasive diagnostic methods was quickly apparent. This led to the development of new techniques such as impedance plethysmography in the 1970's followed by compression ultrasonography, presently the mainstay for the diagnosis of symptomatic deep venous thrombosis. More recently, the potential role of assays to detect D-dimer (degradation product of fibrin) and clinical probability models in the simplification of the diagnostic work-up of patients with suspected deep venous thrombosis have been evaluated. At present several combinations of compression ultrasonography, D-dimer assays and clinical probability assessment have been prospectively validated. Hence, the diagnostic approach in patients with suspected deep venous thrombosis of the leg is now fully non-invasive and markedly simplified, and has been shown to be cost-effective.

In contrast to the rapid advances in the diagnostic management of patients with suspected deep venous thrombosis, the diagnostic management of patients with suspected pulmonary embolism has shown a slower development. As with deep vein thrombosis of the leg, it has repeatedly been shown that only approximately one quarter to one third of patients presenting with clinically suspected pulmonary embolism actually has the disease confirmed upon objective testing. The reference test for pulmonary embolism is pulmonary angiography, an invasive technique that enables the direct visualisation of the pulmonary vasculature. Due to the complications associated with this technique in the years following its introduction and its limited availability, pulmonary angiography never found widespread acceptance in clinical practice. Although the technique has been significantly improved with better catheters and newer contrast media leading to an almost absence of complications, the reluctance to use this method has remained. In 1964 perfusion lung scintigraphy was introduced as a non-invasive technique for the diagno-

sis of pulmonary embolism. Although the diagnostic value of this method was enhanced by the introduction of ventilation lung scintigraphy in 1970, a major drawback of this technique remains the fact that 50-60% of patients has a non-diagnostic scan result, thus requiring further testing (pulmonary angiography) to arrive at a definite diagnosis.
In recent years there have been several promising developments in the area of diagnostic tests for pulmonary embolism. Firstly, spiral computed tomography (spiral CT), a non-invasive technique for the visualisation of the pulmonary vasculature, was introduced in 1992 with the expectation that it could replace conventional angiography. Secondly, analogous to deep venous thrombosis, techniques such as the D-dimer assay, clinical probability models, and compression ultrasonography are being evaluated for their utility in the diagnostic work-up of patients with suspected pulmonary embolism. One of the main problems with the introduction of these techniques has been the limited appreciation for the appropriate steps in the evaluation of new diagnostic methods. This has led to the haphazard introduction of these tests in clinical practice without adequate knowledge of their proper place in the diagnostic work-up of patients with clinically suspected pulmonary embolism.

Outline Thesis Part Two

The second part of this thesis is entitled 'Diagnostics of Pulmonary Embolism'. In **Chapter 9** guidelines for the proper evaluation of diagnostic tests are discussed, analogous to those that must be followed prior to the introduction of new medicines. The most commonly employed diagnostic techniques for pulmonary embolism are thereafter critically reviewed in light of these guidelines. The data presented in the remaining chapters of this thesis are derived from a large, prospective, multi-centre study in consecutive patients with suspected pulmonary embolism, evaluating various diagnostic techniques in comparison with the reference tests (ANTELOPE-Study). It has previously been suggested that the clinical assessment of the probability of disease could guide the diagnostic process. In **Chapter 10** the diagnostic accuracy of various methods for the assessment of the clinical probability (i.e. intuitive and structured assessments) are compared with each other. In recent years many assays for the measurement of D-dimer have been introduced for the exclusion of venous thromboembolism. However, it is largely unknown which of these assays has the best diagnostic accuracy. In **Chapter 11** three quantitative D-dimer assays are compared with each other and subsequently the role of the extent of the embolic disease on the accuracy of the tests is assessed. The negative predictive value and potential clinical utility of a qualitative, bed-side D-dimer assay for exclusion of pulmonary embolism

is examined in **Chapter 12**. In line with the hypothesis of venous thromboembolism being one clinical entity, investigators have suggested compression ultrasonography of the deep veins of the leg for the diagnostic work-up of patients with suspected pulmonary embolism. However, the diagnostic utility of compression ultrasonography has been found to be relatively limited. In **Chapter 13** the accuracy of two methods of performing ultrasonography of the deep veins of the leg (i.e. a limited examination of the femoral vein in the groin and the popliteal vein in the knee versus an extended examination including the superficial femoral vein) are compared with each other. Finally, in **Chapter 14** the cost-effectiveness of several non-invasive diagnostic strategies which have the potential for further improving and simplifying the diagnostic approach in the real clinical setting are evaluated.

References

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