Management of venous thromboembolism. Etiology, diagnosis, prognosis and treatment
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General Introduction

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Many improvements have been achieved in the last decades with regard to the etiological, diagnostic and therapeutic management of venous thromboembolic disease. While 50 years ago its etiology remained unexplained in more than three quarters of the patients, nowadays, as a result of the discovery of an increasing amount of thrombophilic factors, a potential causal factor can be identified in 60 to 80 percent of patients. Until recently, pulmonary angiography and venography of the lower limb were the gold standard diagnostic methods for establishing venous thromboembolism, whereas presently, less invasive diagnostic tests are available to accurately confirm or refute the presence of thrombosis. Also, important progress has been made with respect to the prognosis of patients who have had one or more episodes of venous thromboembolism. Since the introduction of heparin and vitamin K antagonists in the middle of the 20th century, the chance to die as a result of pulmonary embolism has decreased from approximately 25 to four percent. Despite these important advancements, there is still a need for further improvements.

**Etiology**

Investigators in the field of venous thromboembolism cannot ignore the name of Rudolf Virchow. Current insights in the etiology and diagnostic approach of venous thromboembolism are based on concepts developed by this German pathologist already in 1856. The triad he formulated on the pathophysiology of venous thromboembolic disease is still the basis for our understanding of this disease today. Currently appreciated risk factors for the etiology of venous thromboembolism such as immobilisation, surgery and thrombophilia are traced back to Virchow's triad of venous stasis, defects in the vessel wall and changes in blood composition. The knowledge regarding this latter aspect of the triad has expanded enormously in recent times. Since 1965, when Egeberg linked a deficiency of antithrombin to a Norwegian family with a familial tendency towards venous thrombosis, almost all components of the coagulation system have been investigated for their possible contribution to the development of venous thromboembolism. Initially, deficiencies of natural anticoagulant proteins, also called loss of function defects, were investigated as potential risk factors, revealing that deficiencies of protein C and protein S are, like antithrombin, also associated with a higher risk to develop venous thrombosis. However, in not more than ten percent of consecutive patients with venous thrombosis these inherited risk factors were present. Since the discovery that resistance to activated protein C, most often caused by the factor V Leiden mutation, could lead to venous thrombosis, this proportion increased with 20 percent. Recently, thrombophilia research has focussed on the procoagulant proteins as being risk factors for venous thrombosis. In
the latter half of the 1990's, elevated levels of prothrombin, caused by the protrombin-20210A mutation, and high concentrations of factor VIII were recognised as abnormalities that increase the risk of thrombosis. And, more recently, elevated levels of factor IX and XI were shown to be related to an increased risk of venous thrombosis. Finally, the chance to develop thrombosis has been linked to proteins involved in the fibrinolytic system. Thrombin activatable fibrinolysis inhibitor (TAFI) is a procarboxypeptidase which is activated by thrombin and delays fibrinolysis by removing lysine residues that normally serve as binding sites for components of the fibrinolytic system. Decreased levels have been associated with the -438 A allele of the TAFI gene, which in turn is reported to be associated with a lower risk of venous thrombosis. Another coagulation protein important in clot stabilisation is factor XIII, which cross-links fibrin. Recent studies suggested that the factor XIII Val/Leu and Leu/Leu genotypes seem to be associated with a lower risk of venous thrombosis. Since the discovery of all these new etiological factors, the proportion of thrombosis patients in whom such an abnormality can be identified has been increased from less than ten to more than 60 percent.

As is evident from the discussion above, almost the whole coagulation system is unravelled with respect to the influence of each protein on the risk of venous thrombosis. However, several questions remain. Almost all quoted studies were performed in patients with deep venous thrombosis, but not in patients with pulmonary embolism. Despite the fact that these entities both coexist and are now considered to be manifestations of a single disease, it cannot directly be assumed that a thrombophilic factor results in an equal risk of deep venous thrombosis and pulmonary embolism. This is illustrated by the so called factor V Leiden paradox, which refers to the observation that the risk of developing pulmonary embolism is less than half of the risk of getting deep venous thrombosis in carriers of the factor V Leiden mutation, suggesting that this mutation leads to the formation of a more adherent thrombus. The latter hypothesis might be an explanation why some patients present with symptoms of deep venous thrombosis whereas others primarily present with chest symptoms. In chapters 2 and 3 we investigated the effect of elevated plasma levels of the procoagulant proteins IX or XI and the polymorphisms of the TAFI and factor XIII gene on the risk to develop pulmonary embolism. Although an elevated level of factor VIII is an accepted risk factor, it is unknown when to obtain blood for the measurement of the factor VIII concentration, since factor VIII can also be elevated due to an acute phase reaction. In chapter 4 we assessed whether the VIII measurement can be done at the time of presentation with confirmed venous thromboembolism, which is the common time point for a thrombophilia screening, or whether this should be delayed to several months after the acute event. Another open issue concerning the etiology of venous thromboembolism is the question whether travel is associated with an increased risk of deep venous thrombosis and pulmonary embolism.
From the available literature a reliable estimate of this association cannot be obtained. Most studies reported on cases, case series, and just a few controlled studies - only in patients with deep venous thrombosis - are available. Furthermore, they revealed contrasting results. In chapter 5, a prospective study in patients with pulmonary embolism is presented, as well as an extension of our previous study in patients with deep venous thrombosis. Finally, to obtain a more precise estimate of the risk of symptomatic venous thromboembolism among travellers, the results of these three studies were combined in a meta-analysis.

Diagnosis

Another concept of Virchow - which was not taken seriously in his time - regards the nowadays widely accepted view that deep venous thrombosis and pulmonary embolism are manifestations of a single disease entity, i.e. venous thromboembolism. In around 80 percent of patients with symptomatic pulmonary embolism, thrombosis in the deep leg or pelvic veins is present as shown by venographic studies \(^{16-17}\), whereas in 50 to 80 percent of patients with deep venous thrombosis, silent pulmonary embolism can be demonstrated by scintigraphic techniques \(^{18}\). Initially, the diagnostic approaches for deep venous thrombosis and pulmonary embolism were different. In case of suspected deep venous thrombosis venography of the lower limb was performed, while in patients with a suspicion of pulmonary embolism, pulmonary angiography was carried out. Nowadays, the diagnostic management of the two diseases partially overlaps. Another change in the diagnostic approach for deep venous thrombosis and pulmonary embolism is the fact that, given the low prevalence of the disease in consecutive symptomatic patients, two phases are now distinguished. The first phase aims at ruling out the disease with easy to perform non-invasive tests and the second uses imaging techniques with the goal to confirm the presence of thrombosis.

Traditionally, pulmonary angiography and venography of the lower limb were considered the gold standard methods for diagnosing deep venous thrombosis and pulmonary embolism, respectively. Until their introduction, the diagnosis was usually based on clinical signs and symptoms. With the use of these methods, it became clear that only one third of patients appeared to have venous thromboembolism. This stresses the importance of using objective diagnostic methods in case of suspected venous thromboembolism. The clinical diagnosis is not reliable and anticoagulant treatment on the basis of a suspicion is not acceptable because it is associated with a three percent annual risk of major bleeds and a half percent risk of fatal hemorrhage \(^{19}\). Despite the fact that angiography is an accurate method to rule out or confirm venous thromboembolism, it has several disadvantages. It is invasive; physicians are reluctant to use it because of the perceived risks and, it is not readily available.
As a consequence, physicians fail to use this test with the risk of over- or under treatment. Therefore, alternative tests have been investigated of which the following have proven to be useful for the diagnosis of deep venous thrombosis and pulmonary embolism: serial compression ultrasonography of the legs (i.e. a repeat ultrasonogram after 1 week) and ventilation-perfusion scintigraphy, respectively. Presently, serial compression ultrasonography has replaced lower limb venography, whereas ventilation-perfusion scintigraphy has partially replaced pulmonary angiography. However, for serial ultrasonography an extra hospital visit is required, whereas ventilation-perfusion scintigraphy has in around 50% of the cases a non-diagnostic result. Therefore, other candidates for the diagnosis of venous thromboembolism have emerged, which are quick, easy to perform and non-invasive, i.e. the D-dimer blood test and clinical probability estimates. D-dimers are degradation products of cross-linked fibrin, which are elevated in the presence of thrombosis. The D-dimer test is best suitable as a method to rule out venous thromboembolism when normal. The clinical probability estimate, based on information from the medical history and physical examination, can be assessed by either a formal numerical model or an informed intuitive estimate. This test in combination with other diagnostic modalities allows stratification for the likelihood of venous thromboembolism. Presently, the D-dimer test has an established role in the diagnostic approach of patients with suspected deep venous thrombosis. It is used as an adjunct to ultrasonography of the legs, and if both tests are normal, the second ultrasonogram (and an extra hospital visit) can be safely omitted. Probably, even the first ultrasonogram can be omitted when a normal D-dimer test result is combined with a low clinical probability estimate.

We investigated whether this latter combination is also safe in patients with suspected pulmonary embolism (chapter 6). In addition, this chapter evaluates a diagnostic strategy which avoids pulmonary angiography but relies on serial compression ultrasonography of the legs in those with a non-diagnostic ventilation-perfusion scintigraphy result.

Thus, at present, completely non-invasive diagnostic strategies are available for deep venous thrombosis as well as pulmonary embolism which both start with a clinical probability estimate and D-dimer test. However, the usefulness of the D-dimer test in cancer patients, which comprise a substantial proportion of all patients with suspected venous thromboembolism has been questioned. Since D-dimer levels are likely higher in cancer patients, more of these patients will have an abnormal test result making the method less efficient in this population to exclude venous thrombosis at referral. Moreover, the negative predictive value of the test in cancer patients might be lower due to the higher prevalence of venous thromboembolism among cancer patients. Together, the high prevalence of thrombosis among cancer patients and the relatively low specificity of the D-dimer test in these patients will result in a decreased negative predictive value. On the other hand, the
expected lower negative predictive value could theoretically be counterbalanced by an increased sensitivity. In chapter 7 the clinical utility of a whole blood D-dimer test in cancer patients as compared to non-cancer patients with suspected deep venous thrombosis was examined.

Prognosis and Treatment
As with many other diseases, in the past the first therapy for venous thromboembolism consisted of surgery. In 1908 Trendelenburg developed a surgical embolectomy procedure for the treatment of pulmonary embolism \(^4\), whereas Homans in 1934 ligated the femoral vein in a patient with deep venous thrombosis, to prevent pulmonary embolism \(^5\). Nowadays the treatment of choice is mainly pharmacological. Embolectomy is only exceptionally carried out in patients with severe pulmonary embolism accompanied with shock, while instead of venous ligation, caval filters are now applied to prevent pulmonary embolism, but only in special cases, e.g. when anticoagulants are contraindicated. This latter treatment commonly exists of heparin and vitamin K antagonists. Howell and Holt discovered heparin in 1918 \(^6\). They found that two substances, cephalin and heparin, influenced coagulation and twelve years later, heparin was recommended for the treatment of thrombosis \(^7\). The anticoagulant property of the vitamin K antagonist dicumarol was recognised by the veterinary pathologist Schoeffel. He discovered that dying of a fatal hemorrhagic disease in cattle was associated with the intake of spoiled sweet clover \(^8\). Dicumarol was isolated from this clover and from 1941 this was used for the prevention and treatment of venous thromboembolism \(^9\). The first randomised trial of anticoagulants (heparin and the vitamin K antagonist nicoumalone) versus no treatment stems from 1960. This study by Barritt and Jordan was very successful: of the 16 patients randomised to anticoagulants there were no deaths due to pulmonary embolism and no recurrences, whereas in the no treatment control group, five deaths were attributed to pulmonary embolism and another five patients had non-fatal recurrences of pulmonary embolism. Since these results were highly clinically and statistically significant, the trial was stopped prematurely.

Although venous thromboembolism can be effectively treated with (low molecular weight) heparin, vitamin K antagonists and, exceptionally, caval filters or thrombolytic agents, its clinical course is characterised by short-term as well as long-term sequelae. The three to twelve months overall mortality rate of submassive pulmonary embolism varies from one and a half to seven percent, of which most patients will die within two weeks after their initial presentation \(^10-12\). In this period, another five to ten percent of patients will develop non-fatal recurrent venous thromboembolism. If a patient experiences recurrent venous thromboembolism, the case-fatality rate has been estimated to be approximately 26% \(^13\). As far as long-term sequelae are concerned, in half of the patients who have
had deep venous thrombosis, the post-thrombotic syndrome will occur in the two to three years following the initial event. The absolute risk of recurrent deep venous thrombosis will accumulate over an eight-year period to 30 percent \(^4\). Less is known about the long-term sequelae of pulmonary embolism, but it is estimated that a few percent of patients who suffered from pulmonary embolism will develop chronic thromboembolic pulmonary hypertension \(^4\). In order to reduce the short- and long-term thromboembolic complications there is renewed interest in the possibility to treat patients with pulmonary embolism more aggressively \(^4\)-\(^8\). In chapter 8 a meta-analysis is presented of studies evaluating the efficacy and safety of thrombolysis versus heparin for the initial treatment of deep venous thrombosis and pulmonary embolism.

At present, standard treatment for deep venous thrombosis or pulmonary embolism consists of an initial course of (low molecular weight) heparin for at least five days and subsequently vitamin K antagonists for three to six months. It is recommended to treat massive pulmonary embolism associated with systemic hypotension - which has a high mortality of approximately 18 percent \(^9\) - more aggressively. Risk stratification for selection of this latter patient category is based on clinical signs and symptoms. In patients with pulmonary embolism and circulatory collapse, thrombolysis is the therapy of choice \(^{10}-^{14}\). Some experts advocate a broadening of the indication for thrombolytic therapy. They advice, in addition to hypotensive patients, to also treat hemodynamically stable patients with echocardiographic right ventricular dysfunction \(^{15}-^{17}\). Others believe that exposure to thrombolysis in these patients will result in unnecessary deaths and intracranial bleeds \(^{18}-^{22}\). Before it is justified to treat patients with fibrinolytic therapy, the prognostic significance of echocardiographically assessed right ventricular dysfunction for the prognosis of patients with acute pulmonary embolism needs to be established. The systemic review presented in chapter 9 aims to answer the question whether echocardiographic right ventricular dysfunction is a prevalent and independent prognostic indicator of short- and long-term pulmonary embolism related mortality in patients with acute pulmonary embolism. Another potential test for risk stratification is an easy to perform blood test for measurement of plasma brain natriuretic peptide (BNP). BNP is a neurohormone with diuretic and vasodilatory properties that is secreted by the cardiac ventricles in response to stretch and/or pressure increase. Elevated levels of BNP are sensitive for congestive heart failure \(^{23}\) and seem to correlate with right ventricular dysfunction \(^{24}\). Chapter 10 presents the results of a study investigating this novel potential predictor for adverse outcome in patients with acute pulmonary embolism.
References


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