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**Title:** Are pulmonary embolism and deep-vein thrombosis always one disease?  
**Date:** 2012-09-11
CHAPTER 1

General introduction
INTRODUCTION TO VENOUS THROMBOSIS AND ITS DIAGNOSIS

Pulmonary embolism is traditionally, since autopsy studies by Virchow in the mid 1800s, thought to originate from embolization of a deep-vein thrombosis, resulting in two clinical manifestations of one disease: venous thrombosis. The incidence of deep-vein thrombosis in the population is twice as high as the incidence of pulmonary embolism, i.e. 1 per 1000 and 0.5 per 1000 person-years respectively. Clinical symptoms of deep-vein thrombosis range from mild pain in the legs to chronic complaints, as in postthrombotic syndrome. In pulmonary embolism, presentations range from dyspnea and chest pain to hemodynamic instability and sometimes acute death. Pulmonary embolism is one of the common causes of cardiovascular death. The mortality rate of acute pulmonary embolism (15% at 3 months) exceeds the mortality rate of acute myocardial infarction. Not all patients who present with pulmonary embolism have symptoms of the legs, i.e., a concomitant deep-vein thrombosis. Vice versa, only a fraction of patients with deep-vein thrombosis has dyspnea or chest pain.

At present, the first line imaging modality for suspected pulmonary embolism is CT pulmonary angiography. Emboli on CT are visible as contrast filling defects in the pulmonary arteries. Despite its excellent sensitivity and specificity, disadvantages of CT pulmonary angiography are exposure to radiation and the need for iodinated contrast. For deep-vein thrombosis of the legs, ultrasonography is the diagnostic modality of choice. Compared with the gold standard, contrast venography, ultrasonography has a sensitivity of 96% and a specificity of 98% for the detection of proximal symptomatic deep-vein thrombosis. For imaging of below knee thrombi and pelvic thrombi, ultrasonography is less reliable. False positive findings tend to increase more distally.

INITIATION OF A VENOUS CLOT IN THE VALVE SINUS

Three main mechanisms that contribute to thrombus formation have been described by Rudolf Virchow in his well-known triad: stasis of venous blood, changes in blood composition (nowadays known as thrombophilia), and damage to the vessel wall. The vessel wall has been studied extensively in arterial disease. When atherosclerotic plaques within arterial walls rupture, this results in arterial thrombosis such as myocardial infarction. On the venous side the situation is very different, however, and research on the venous vessel wall is scarce. Venous clots are not related to cholesterol plaques, nor can they be treated with antiplatelet or cholesterol lowering drugs. The venous vessel wall is thinner and contains less smooth muscle cells than the arterial wall; more importantly veins contain valves that regulate blood return to the heart. These venous valves have first been described by Fabricius in 1603 (Figure 1), work that was further developed by Harvey, who became famous for his ideas on a closed circulation as opposed to the concept that blood is consumed after being pumped out of the heart (“De motu cordis”,...
1628). Figure 2 shows a drawing by Harvey to prove that veins were needed for returning blood to the heart.

More recently, the valves have been described functionally and morphologically. Human valves are bicuspid, and are positioned in a valve sinus, a local widening of the venous wall. The area between a valve leaflet and the vessel wall is called the valve pocket and is regarded as the place where thrombi originate (Figure 3). Stasis of blood in the pocket predisposes to thrombus formation. In the deepest part of the valve pockets, blood circulates with very low velocities in so called vortices, creating a low shear field, allowing red cells to aggregate. Stagnation of blood leads to hypoxia, which subsequently causes endothelial damage and activation of the coagulation system.

**Does Pulmonary Embolism Always Start as Deep-Vein Thrombosis?**

Now that we know where thrombi originate, one of the central questions addressed in this thesis is whether pulmonary embolism always starts as deep-vein thrombosis or not. In 20 to 50% of patients with pulmonary embolism, no deep-vein thrombosis could be found on an ultrasonography examination. One explanation could be that calf veins and pelvic veins are an overlooked source of pulmonary embolism in ultrasonography.
imaging. Therefore, other imaging modalities may lead to a larger yield of deep-vein thrombi either in the abdominal and pelvic region, or in the calf veins. Thrombi in the calf veins extend to proximal veins in 20 to 30% of cases, so their contribution towards pulmonary embolism is not negligible.12

We aimed to search for the missing deep-vein thrombi in patients with a pulmonary embolism by using a novel total body imaging technique: Magnetic Resonance Direct Thrombus Imaging (MRDTI). This technique is based on endogenous contrast present in the blood clot as methemoglobin. A high signal can be detected using a 3D gradient-echo technique, with T1-weighting.13

Another explanation is that not all pulmonary emboli are accompanied by a deep-vein thrombosis. In those cases, a different origin of pulmonary embolism needs to be thought of, such as cardiac thrombi in patients with atrial fibrillation.

Figure 2. William Harvey showed the presence of veins with valves in the forearm, and grasped their function.
Are risk factors for pulmonary embolism different than for deep-vein thrombosis?

When we consider deep-vein thrombosis and pulmonary embolism to be two manifestations of the same disease, we would expect risk factors to be identical. However, when we study risk factors for deep-vein thrombosis and pulmonary embolism, we find some striking differences. The best established difference is called the factor V Leiden paradox. The presence of the factor V mutation gives a higher risk for deep-vein thrombosis than for pulmonary embolism, which has been confirmed in numerous study populations. An example of an acquired risk factor that differs for deep-vein thrombosis and pulmonary embolism is the oral contraceptive pill. Use of the pill gave a 4-fold increased risk of pulmonary embolism, and a 7-fold increased risk of deep-vein thrombosis versus healthy controls in the MEGA case-control study. In this thesis, the factor V Leiden paradox is broadened by comparing effect sizes of both acquired and genetic risk factors for deep-vein thrombosis with the effect sizes for pulmonary embolism.

Figure 3. The anatomy of a venous valve (schematic).

a. The valve is open, and blood flows toward the heart, in part due to contractions of the lower-leg muscles.

b. The valve is closed, blocking retrograde flow and ensuring the continuous flow of blood toward the heart. Valve closing occurs with each valvular cycle and is most marked during pulsatile, calf muscle-driven flow.

DESCRIPTION OF CLINICAL STUDIES IN THIS THESIS

The results described in this thesis are based on three different study populations: the PEDLAR study, the Aging venous valves study, and the MEGA study.

PEDLAR study

The acronym ‘PEDLAR’ stands for Pulmonary Embolism: Development, Localization and Risk factors. The study aims were to find the anatomical origin of a pulmonary embolism and to compare genetic and acquired risk factors in pulmonary embolism and deep-vein thrombosis patients. In the PEDLAR study, patients with a radiologically confirmed first venous thrombotic event (100 with deep-vein thrombosis and 100 with pulmonary embolism), were asked to undergo a total body MRDTI scan within a week after diagnosis. Patients were enrolled from two hospitals: the Leiden University Medical Center and the Rijnland hospital in Leiderdorp. Besides imaging, the protocol involved DNA collection to test for the factor V Leiden and prothrombin mutation, and a questionnaire on common acquired risk factors for thrombosis. Inclusion started in October 2008 and was completed in March 2011.

Aging venous valves study

Increasing age is a strong risk factor for venous thrombosis. At present, biological explanations are being sought to clarify this increased risk with age. Elderly persons are often more immobilized than younger persons, and are affected by more comorbidities, such as malignancies or bone fractures. These conditions are in themselves risk factors for venous thrombosis. Furthermore, calf muscles that are essential in the return of venous blood to the heart become less compliant in the elderly. With aging, cell repair decreases. This occurs in the venous vessel wall as well. In the veins there are bicuspid valves that function as flow modulators to maintain constant blood supply to the right heart. Previous studies in the field of pathology have shown that these valves become thicker with age. The increase is due to the presence of collagen, both in the vessel wall and the valve leaflets. In our in vivo study we enrolled healthy volunteers without a history of deep-vein thrombosis or pulmonary embolism. An ultrasonography examination was done to measure valve thickness and valve function with age. Participants were aged between 20 to 80 years.

MEGA study

MEGA stands for Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis. The MEGA study is a population-based case-control study. Participants were aged 18 to 70 years. 4956 consecutive patients with deep-vein thrombosis or pulmonary embolism were enrolled from six anticoagulation clinics in the Netherlands, together with 6297 age- and sex-matched controls. A questionnaire was filled in for
assessment of risk factors for venous thrombosis. In addition, participants provided a blood or buccal swab sample for DNA. Common genetic risk factors were assessed, e.g. the factor V Leiden mutation, prothrombin G20210A and ABO-blood group.

**OUTLINE OF THIS THESIS**

In Chapter 2, we elaborate on the differences between causes of pulmonary embolism and deep-vein thrombosis, by studying their relation with genetic and acquired risk factors in a review based on a broad literature search. In case no information was present in literature, risk factors were also stratified for type of thrombotic event in the MEGA case-control study.

Chapter 3 gives an overview of the state of the art imaging techniques for venous thrombosis. Here, the focus lies on MRI techniques that have been developed for thrombus imaging. Future directions, such as the use of fibrin labeling as a new contrast agent are discussed.

Chapter 4 describes a study comprising ultrasonographical assessment of the venous valves. Our aim was to measure valve leaflet thickness in relation to age. We hypothesized that part of the increasing incidence in venous thrombosis with age can be explained by increasing valve thickness.

Chapter 5 presents data on patients from the PEDLAR study, where we search for the origin of pulmonary embolism using a total body MR thrombus imaging technique. We propose several mechanisms for the absence of deep-vein thrombi in more than half of the patients with pulmonary embolism.

In Chapter 6 we relate pulmonary embolism severity on CT pulmonary angiography to deep-vein thrombosis extent on MRI. The Qanadli score and right ventricle/left ventricle diameter ratio were used as indicators of pulmonary artery obstruction and pulmonary embolism severity, respectively.

Chapter 7 explores differences between pulmonary embolism and deep-vein thrombosis regarding thrombus location, and thrombus extent (expressed as thrombus length and number of affected veins), as assessed on MRI.

In Chapter 8 we assess clinically diagnosed superficial vein thrombosis as a risk factor for venous thrombosis. This analysis was performed on data from the MEGA case-control study.

Finally, in Chapter 9 we give an overview of the current performance of CT pulmonary angiography in a population of patients with suspected pulmonary embolism in the Leiden area. We aimed to describe the CT pulmonary angiography yield by evaluating both the percentage of CTs with confirmed pulmonary embolism, and the percentage of CTs without any finding, related to patient characteristics and referral site.