Physical activity, immobilization and the risk of venous thrombosis

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Chapter 1

Introduction

Venous thrombosis is a common disease affecting millions of individuals every year[1]. Approximately 80 percent of the thrombi originate in the leg. Thrombi can detach resulting in a pulmonary embolism. This embolism is fatal in approximately 10 percent of the cases[2]. Most patients with a fatal pulmonary embolism die within two hours after the onset of the symptoms[3]. For this reason, it is important to focus on the identification of risk factors as this may lead to the prevention of venous thrombosis. In 1856, Virchow described thrombosis as a disease caused by clotting of the blood[4]. He wrote "Wir können auch künftig die mehr mechanische Formen der Thrombose, wie sie bei der Blutstockung vorkommen [*stasis*], von den mehr chemischien [*blood composition*] or physikalischen Formen, wie sie durch direkte Sauerstoff-Einwirkung oder veränderte Flächenanziehung zu Stande kommen [*vessel wall*], unterscheiden". This has been interpreted as the now famous "Triad" with three major causes of thrombosis e.g. slowing down of the bloodstream the so-called stasis, changes in the blood composition and damage to the vessel wall. It is generally believed that only the first two causes are involved in the occurrence of venous thrombosis.

As humans walk upright, blood from the feet and lower legs has to overcome gravity for over a meter before it reaches the heart. It is therefore easy to imagine how stasis occurs in the veins of the lower extremities. This may lead to the formation of blood clots in the bloodstream. Two important systems assist the blood in streaming upwards. First, veins contain valves which prevent the reflux of blood after it passes the valves. When the valves are damaged, due to for example varicose veins, the risk of venous thrombosis increases[5]. Secondly, the blood flow is stimulated by the pump function of the leg muscles. Altered muscle function due to immobilization is known to cause venous thrombosis. In the Second World War, increased rates of pulmonary embolism were reported in individuals who had sought shelter in the underground and had sat cramped positions for hours during the bombings on London[6] (see figure 1). Nowadays more "modern" forms of immobilization have been reported to cause venous thrombosis such as the economy class syndrome due to travel in airplanes[7] and "eThrombosis" due to extended periods of computer work[8].

Figure 1. People sheltering from air raids in the Aldwych underground station, London, UK.

Stimulation of the blood flow by increasing calf muscle movement through physical activity is therefore likely to decrease the risk of venous thrombosis. Mild forms of physical activity such as ambulation after surgery or giving birth may reduce the risk of venous thrombosis. In the early 1900s women were advised to stay in bed for 28 days after delivery[9] and venous thrombosis rates post-partum were very high; up to 8 per 1000 deliveries[10]. Nowadays, women usually leave the bed on the same day as the delivery and venous thrombosis rates post-partum have decreased to approximately 1 per 1000 births[11;12]. Although many other factors have changed since then, these figures suggest that ambulation soon after delivery decreases the risk of venous thrombosis. Up till now, it was unknown whether the drop in venous thrombosis rates was actually due to the change in ambulation policy. Therefore the reasons and implications of this transition will be described in **chapter 2.**

Besides ambulation more rigorous forms of physical activity such as sports activities may affect the risk of venous thrombosis. Only a few studies have been conducted on this association and conflicting results have been found. One cohort study has shown increased venous thrombosis rates after sports activities[13], while a case-control study has shown a decreased incidence of venous thrombosis[14]. Conflicting results are also found in the

composition of the blood in relation to physical activity. On one hand, during and shortly after exercise the blood is in a procoagulant state[15;16]. However, after a training period of several months daily levels of procoagulant factors are reduced and there is less of a prohrombotic state than in individuals who are untrained[17;18]. This suggests that performing sports activities on a regular basis results in a beneficial coagulant balance that may reduce the risk of venous thrombosis. However, performing sports activities also increases the risk of injuries[19] which may result in immobilization and lead to venous thrombosis. Up till now not much was known on the association of sports activities and venous thrombosis risk. For this reason the risk of venous thrombosis associated with sports activities was determined in two separate studies. Results from a case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study), are described in **chapter 3**. The results obtained in a cohort study (Cardiovascular Health Study or CHS) are described in **chapter 4.**

The physicians Sir James Paget (London, 1875)[20] and Leopold von Schrötter (Vienna, 1884) described a second mechanism for an increased risk of venous thrombosis after sports activities, which is called the Paget-Schrötter syndrome[21] or effort induced thrombosis. It was later shown that overdevelopment of the scalene muscle can compress the subclavian vein resulting in a rare form of venous thrombosis, i.e. venous thrombosis of the arm (figure 2). Many case reports of venous thrombosis of the arm have been published regarding athletes who intensively use their arms, such as weight lifters[22] and wrestlers[23]. So far risk estimates for performing sports involving the arms have not been made. Therefore in **chapter 5,** we assessed whether arm sports increase the risk of venous thrombosis of the arm compared with sports mainly involving the leg and performing no sports at all.

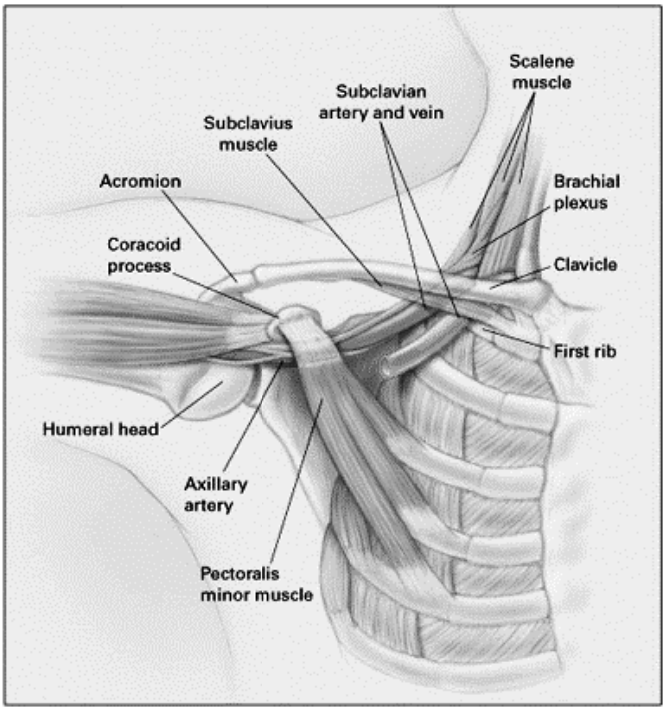

Figure 2. The Paget-Schrötter syndrome; the subclavian artery, vein and scalene muscle all are fixed between the clavicle and first rib. Overdevelopment of the scalene muscle therefore leads to compression of the vein, as the artery can not be compressed. This results in decreased blood flow through the vein and could therefore lead to venous thrombosis of the arm.

As described previously, sports activities may lead to injuries which can increase the risk of venous thrombosis. Major trauma, for example as caused by car accidents, has long been known to increase venous thrombosis risk to a large extent. Autopsy studies in the 1930s showed that pulmonary embolism was the cause of death in 38 percent of fatal injuries[24]. Without prophylaxis, venous thrombosis, mainly asymptomatic, occurred in approximately half of the trauma patients[25]. For this reason, many patients with major injuries who are hospitalized, have surgery or plaster cast are provided prophylactic anticoagulant treatment. However, not much is known about the effect of minor injuries that do not require hospitalization. In general, when someone has an ankle sprain or knee twist, no prophylaxis is provided. As it is unclear what the risk is and whether this regimen is appropriate, the association of minor injuries with the risk of venous thrombosis was studied in **chapter 6**.

Finally, some risk factors have been shown to differentially affect the risk of deep vein thrombosis of the leg and pulmonary embolism. Factor V Leiden, a genetic risk factor for venous thrombosis, has a clear effect on the risk of deep venous thrombosis but little or no effect on pulmonary embolism risk [26;27]. Several causes for this difference have been proposed and will be studied in **chapter 7**. Mechanisms under study are, among others, an effect of the factor V Leiden mutation on the location of the thrombus in the leg, the number of affected veins, and the speed of thrombus formation i.e. the time between the formation of the thrombus and the actual diagnosis.

In the final chapter, **chapter 8**, the results in this thesis will be summarized and their validity and implications will be discussed. Furthermore, some suggestions for additional research will be presented.

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