Physical activity, immobilization and the risk of venous thrombosis

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Cover: Motionless water in a pool made for physical activity
Cover design: K.J. van Stralen & J. van der Ahé

Lay-Out: Y. Souverein

ISBN: 978-90-9022857-0

Printed by Gildeprint, Enschede, the Netherlands

Physical activity, immobilization and the risk of venous thrombosis

Proefschrift

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,

op gezag van Rector Magnificus prof.mr. P.F. van der Heijden,

volgens besluit van het College voor Promoties

te verdedigen op donderdag 3 april 2008

klokke 15.00 uur door

Karlijn Janneke van Stralen

geboren te Delft

in 1980

Promotiecommissie

Promotor: Prof. Dr. F.R. Rosendaal

Copromotor: Dr. C.J.M. Doggen

Referent: Prof. Dr. B.M. Psaty (University of Washington, Seattle, USA)

Overige leden: Prof. Dr. J.P. Vandenbroucke
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Dr. S. Le Cessie

The work described in this thesis was performed at the department of clinical epidemiology, Leiden University Medical Center, Leiden, the Netherlands, and the Cardiovascular Health and Research Unit, University of Washington, Seattle, USA. This research was supported by the Netherlands Organization for Scientific Research (912-033| 2003) and the Leducq foundation, Paris, France for the development of transatlantic networks of excellence in cardiovascular research.

Financial support by the Netherlands Heart Foundation and the J.E. Jurriaanse Stichting for the publication of this thesis is gratefully acknowledged.

Additional support was kindly provided by Bayer Health Care and Roche Diagnostics.

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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.

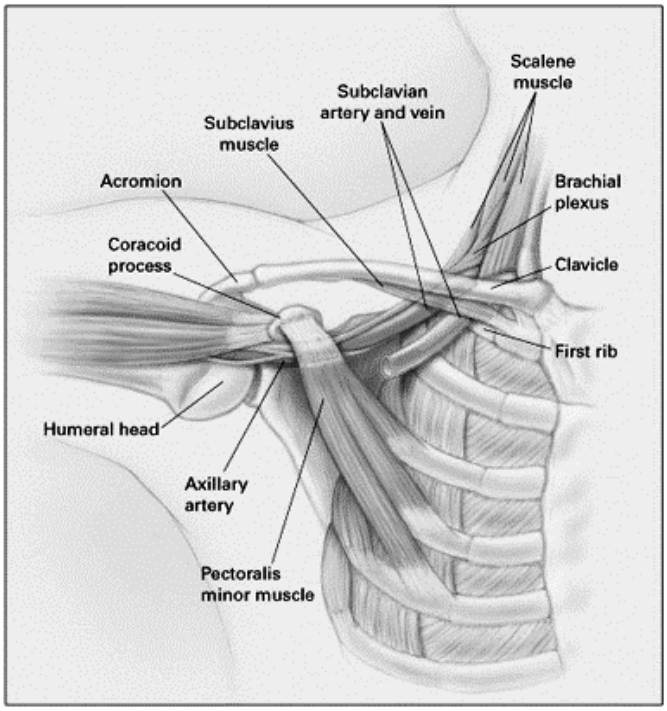

Figure 2. The Paget-Schrötter syndrome; the subclavian artery, vein and scalene muscle all are fixed between the clavicle and first rib. Overdevelopment of the scalene muscle therefore leads to compression of the vein, as the artery can not be compressed. This results in decreased blood flow through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

The tortuous history of the implementation of early ambulation after delivery.

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Journal of the Royal Society of Medicine, 2007 feb; 100 (2):90-96

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Abstract

At the beginning of the twentieth century, venous thrombosis was a major complication during puerperium. It occurred in almost eight out of 1000 postnatal women and was fatal in about a third of the cases. Around 1900 women were told to stay in bed until the 28th day. Nowadays women are advised to get out of bed as early as possible in order to prevent thrombosis. We therefore studied what led to early mobilisation after delivery.

Published studies identified via searches of literature databases MEDLINE, EMBASE, Web of Science, Scopus, Index Medicus, Dutch Central Catalogue, consecutive editions of generally used British, American and Dutch obstetrics and gynaecology textbooks, old volumes of The Lancet and the Dutch 'Nederlands Tijdschrift voor Geneeskunde'

In 1878, the German gynaecologist Küstner promoted early ambulation, which was embraced by other German gynaecologists. After a short period of cautious implementation, the practice of early mobilisation disappeared. This was due to new theoretical arguments and anecdotal cases of fatal pulmonary embolisms upon mobilisation. The Second World War and the baby-boom meant that there was pressure on hospital maternity beds, resulting in practical reasons for early discharge of the mother. After WWII the reserved attitude against early ambulation began to disappear. Nevertheless, it took until the 1980s before the practice of early mobilisation was universally applied.

Even though a reduction in venous thrombosis and overall morbidity were the primary reasons for implementation of early ambulation, no accurate risk estimations of its effect have been made. The final implementation was mainly due to practical reasons.

Introduction

One of earliest known risk factors for venous thrombosis is pregnancy. As long ago as 1718 Mauriceau described the "milk leg". He suspected that in pregnant women a venous thrombosis in the leg was caused by "redundancy and metastasis" of breast milk causing the swelling and pain.[1,2] This idea lasted for more than a century and is generally accepted as the first description of a venous thrombosis.[2] It was not until the 1850s that people realised venous thrombosis was not only a disease of women during or after pregnancy.[2] By the beginning of the 20th century venous thrombosis occurred in approximately eight out of 1000 women who had just given birth and was fatal in about a third of the cases.[3]

For a long period, even until after the Second World War, most clinicians believed that venous thrombosis was an infectious disease and could be contagious.[4] In 1856 Virchow described venous thrombosis as a disease caused by clotting of the blood.[5] He developed the now famous 'Triad of Virchow' in which he described three major causes for venous thrombosis - damage to the vessel wall, changes in the blood composition, and slowing down of the bloodstream. Currently it is believed that the latter two risk factors are the most important for venous thrombosis. During pregnancy and shortly after delivery coagulation factors are increased which ensures that bleeding during delivery is not prolonged.[6] At the end of the pregnancy, the velocity of the bloodstream also falls by 50 % [7,8] due to compression of the inferior vena cava.[7,9] To ensure that the circulation returns to normal after childbirth, women are nowadays stimulated to get out of bed as early as possible. However, even though stasis had been postulated as a potential cause of venous thrombosis as early as 1856, early ambulation only became widely accepted after the Second World War, whilst immediate ambulation after delivery has only become a general rule since the 1980s. In the Netherlands gymnastic exercises starts on the first day after delivery.[10] Women are advised to get out of bed early and bruises, piles, and stitches are no reason not to participate. After a caesarean delivery exercises start on day two.[10]

Given that Virchow postulated the risk of venous stasis in 1856, and pregnancy was known to be an important risk factor for venous thrombosis, why was it not until the 1980s before early ambulation after delivery was generally implemented in hospitals? On what evidence was early mobilisation based? These questions are the focus of our extensive literature search, the results of which are reported here.

Methods

A literature search was being performed using Medline containing one of the following words: pregnancy, puerperium, postpartum, post-partum, obstetric*, maternity, in combination with either ambulation, mobilisation, mobilization, bed rest, bedrest, exercise, move, moved, rise, rising or discharge. Medline was also checked for entries for “milk leg” and “phlegmasia alba dolens”. Similar terms were used in other bibliographic databases such as Embase, Web of Science, Scopus, and two journals, the Dutch “Nederlands

Tijdschrift voor Geneeskunde" and The Lancet. Furthermore, Index Medicus (1879-1950), and the Dutch Central Catalogue were searched using the terms gynaecology, gynaecologie, obstetrics and verloskunde. References cited in other articles were checked. Whenever available, German, English, French, Dutch and Czech articles were read in their original language. Consecutive editions of widely used American, British and Dutch obstetrics and gynaecology textbooks, published between 1930 and 1975, were read and references cited in these books were traced if the topic concerned immobilisation after childbirth. We interviewed well-known Dutch obstetricians, namely Prof. Dr J.F. Schutte (in practice from 1930 to 1975) and Prof. Dr H.J. Huisjes (in practice from 1960 to 1990), Prof. Dr P.E. Treffers (who remains in practice, having started in 1965), and Prof. Dr J. Bennebroek-Gravenhorst (who remains in practise, having started in 1968). Most research in obstetrics and gynaecology at the end of the 19th and beginning of the 20th century was performed in Germany and other European countries. The discussion emerged in the US literature only shortly before the Second World War.

1777 to First World War

In 1777 an English obstetrician, by the name of Charles White, in his treatise on the Arrest of Puerperal Fever, recommended early mobilisation after delivery.[2,11] However this recommendation was not followed by other obstetricians and disappeared.[2,12] Gooch, also from Great Britain, held the opposite opinion in 1820; this professor of obstetrics cautioned his student obstetricians not to allow their patients out of bed before the 21st day after delivery.[11] At the end of the 19th century women were advised to stay in bed for 28 days.[13] Around 1900 German gynaecologists started early mobilisation. This was based on the finding of Küstner in 1878.[14,15] He wanted to reduce the risk of infection in women after childbirth. He wondered whether this risk could be reduced if women had the same "bed regimen" after giving birth as healthy individuals, so he decided to encourage women to get out of bed at an early stage. He found less fever in these women and moreover did not find any deep venous thrombosis in 600 women who were mobilised on the first day after delivery, when eight cases would have been expected.[16] After this promising result other German obstetricians started to mobilise women at an early stage. The firsts to follow were Krönig and Bumm, who also reported beneficial results.[2,17-20] In 1902 Krönig found that in

a group of 416 women in his maternity clinic who were mobilized on the first day, no venous thrombosis or pulmonary embolism occurred (0 %). Amongst 146 women who stayed in until at least the 11th day, five had a venous thrombotic event (3.4%).[2] This led to the suggestion by Krönig that venous thrombosis was mainly caused by disturbances of the circulation.[16]

Bumm confirmed these results in 1907; he did not find any venous thrombosis among 900 women mobilized early.[2,16] Around 1911, Klein found no cases of venous thrombosis in 2524 women who were mobilized between the first and third day, whereas in 2500 women who stayed in bed until at least the ninth day, four venous thromboses and one fatal pulmonary embolism occurred.[2] Gauss found similar results among 600 women. He did not find a single case of venous thrombosis among women who had been mobilized early, compared with eight cases of venous thrombosis among the women who had remained in bed for at least six days, however it is not known how many women remained in bed for that period.[16] In all these studies, however relatively healthy women were allowed out of bed at an early stage, while the women who had fever and other complications were generally kept in bed for a longer period.

After these results many clinics, mainly German, adopted early mobilization, although every clinic had its own definition of early ambulation. While one clinic advised its patients to get out of bed on the first day after delivery, other clinics still spoke of "early ambulation" when women stayed in bed until the eighth day.[2] Prevention of venous thrombosis was not always the reason for early ambulation. In 1908, Hüffell, for example, mobilised his relatively healthy patients after four days to make it easier for them to return to daily life.[16] Before this change in practice, women were required to stay in bed until the eight day and went home the ninth day. At home the daily activities had to be resumed leaving women little time to re-acclimatise to normal life.[16]

Besides the positive effects of prevention of venous thrombosis and acclimatisation, some physicians like Hüffell[16], Velits[18], Simon[21] and Alvensleben[20] also saw other beneficial effects of early ambulation on general morbidity.[16,21] Among these postulated effects were more rapid involution of the uterus and genitals,[2,18] fewer uterine prolapses and

retroflexions, [16,21] less fever,[18] fewer pneumonias,[2] less blood in the lochia[18] and a better state of mind[2].

Despite these beneficial results in the early 1900s, European obstetricians became more careful in prescribing early ambulation after 1910. Four important reasons accounted for their reluctance. The main reason was that the abdominal organs were thought to be loosened by childbirth, and would put too much pressure on the uterus, increasing the risk of prolapses (Huisjes, Schutte, personal communication [11]). Our review of the literature did not show any evidence that staying in bed prevented prolapses. However, until long after the Second World War, this was the main reason for not to implementing early ambulation.[22]

A second reason was a publication by Fromme, head of the university maternity clinic in Halle, Germany. He described a single lethal case of pulmonary embolism due to, in his opinion, premature ambulation.[17] In 1908, after the experiences of Krönig and others, he had allowed women without fever or other complications to sit up in bed on the first day. One early ambulated woman died of a severe pulmonary embolism shortly after early mobilization. Since Fromme had never seen a lethal pulmonary embolism among his 6600 patients who had the old bed rest policy, he strongly advised caution in promoting early ambulation until more was known on the cause of pulmonary emboli.[17] This report was influential: most obstetricians acted less enthusiastically in prescribing early ambulation after delivery.[19] A third reason was that, although some German gynaecologists were convinced of the beneficial effects of early ambulation, some were afraid that a policy change would force women from the working class to return to their usual physical activities too early.[12,20,21] Finally, not all gynaecologists were convinced of the beneficial effects of early ambulation, as in most studies only the healthy women were allowed to get out of bed early.[21]

Gynaecologists in the United States were also reticent about early ambulation. In 1910 Mosher surveyed views about early ambulation among many important American obstetricians.[12] Most obstetricians did not allow women to get out of bed before the tenth day. However, compared to Great Britain and the Netherlands, women were more often

allowed to move freely in bed and to eat in the sitting position.[12,23,24] Most clinicians in the United States had heard about the German practice. Nevertheless, they did not believe it would be useful and they thought it could be dangerous. They reasoned that “as the practice (by White) did not find many imitators, it was not found advantageous”.[12] The appearance of several cases of lethal pulmonary emboli and the ideas that "rest is best" and "the American women of the better class were no comparison to the German peasantry" (Mosher, page 624) resulted in a more conservative approach in the United States.[12]

First to Second World War

Probably the first semi-randomised controlled trial for women during puerperium was proposed by Baird around 1930 when he worked as an assistant obstetrician in Glasgow, Great Britain. The legs of the women in that hospital were tied together for 14 days to prevent infection. Baird questioned the rationale of this regime and proposed that he might try, on alternate women after giving birth, not to tie the legs with binders and see what would happen.[25,26] According to one textbook, subsequent comparison of these women with those who had their knees tied did not show a benefit of tying the legs and the practice was discontinued.[26] However a second textbook suggests that this experiment was only proposed by Baird and that it is uncertain whether it was performed.[25]

Wichmann wrote in 1938 a manuscript promoting early ambulation after surgery and delivery.[19,27] He obtained his ideas from the studies done by Küstner and Krönig, as well as new studies done by Scherf.[19] Scherf had found in an autopsy series that deep veins were more often thrombotic in women who had a long bed rest compared to those with a short bed rest.[19] Wichmann implemented early ambulation in his clinic and saw many beneficial effects. Women themselves preferred it, and less overall morbidity was found. Eight months after the policy change not a single woman had experienced a venous thrombosis or pulmonary embolism.[19] In Helsinki, Finland, 4447 out of 4657 women were allowed out of bed within 48 hours after delivery between January 1938 and June 1939. Fewer cases of venous thrombosis (0.11%) were found compared to women who had to remain in bed for the usual length of time (0.41%) after delivery between 1927 and 1936.[11,27]

For a long time after the Second World War gynaecologists and obstetricians faced a dilemma. As it was becoming more and more accepted that early ambulation prevented the risk of venous thrombosis, they were also afraid that premature ambulation might lead to increased risks of prolapses of the uterus, bladder and even rectum (Huisjes, Bennebroek-Gravenhorst, personal communication[28]). This dilemma resulted in different approaches in different countries and hospitals. After a plea by Chalier, an advocate of early ambulation, a group of French clinics implemented early ambulation in the late 1930s.[19] In Britain and the United States it was usual to let the women stay in bed for approximately 7 to 14 days, however women were allowed to move freely in bed.[29-33] A remarkable fact is that gynaecologists in these countries did not advise elastoplast strapping or binders anymore, whilst in the Netherlands this was still common practice.

Second World War to 1950

New reasons to practice early ambulation arose during the Second World War. During the Blitz in 1940, women in a maternity hospital in London were encouraged to get out of bed on the first day, so that in case of a bombing they would be able to walk to the air-raid shelter themselves. Less morbidity, better involution and considerable less venous thrombosis occurred, although the latter was ascribed to the increased use of elastoplast strapping. It was believed that "a possible increased risk of prolapse was justified under these unusual circumstances".[34]

In the United States a shortage of hospital beds occurred in the beginning of the Second World War. A wartime baby boom occurred, because women wanted to have children by their husbands before they went overseas. This resulted in an increase in births from 18.4 per 1000 population in the 1930s to 22.7 per 1000 at the height of the baby boom in 1943.[35,36] The shortage of hospital beds became even more problematic, as not only rich women delivered in hospital, but other social classes could also afford a hospital stay. In 1935, 24.4% of the births took place in hospital, while this increased to 78.8% in 1945. Supported by findings of the London hospitals during the Blitz, the only way to solve the shortage problem was believed to be early discharge. However, since early discharge was affecting not only lower economic classes but also the middle classes, physicians had to

show that early ambulation was safe. In a hospital in Baltimore 150 women with no complications after normal childbirth were allowed out of bed on the third or fourth day postpartum. Women who got out of bed earlier, had better involution and a similar morbidity rate compared women with similar characteristics in a second hospital, in which the old bed rest regimen was practiced.[11,36]

The baby boom in Europe started after the Second World War, but it resulted in the same problems as had been experienced a few years earlier in the United States. In Britain there were too few maternity beds in hospital. As women were sent home on the fifth day it was important that they were able to do easy tasks themselves.[37] Half a day after delivery, women were stimulated to sit on the bedside and move their legs. Both physicians and patients eagerly accepted this policy. A survey showed that most general practitioners (69%) were in favour of early ambulation.[37] No differences in the occurrence of venous thrombosis were found in the new practice compared to the old regimen.[37]

Even though the acute shortage of hospital beds was an important problem for hospitals, not all agreed with the idea of early discharge. Hospitals were advised in the Journal of the American Medical Association not to discharge patients before the seventh or eight day and with printed instructions about their future care.[38]

1950 to 1980

Around 1950 the attitude of physicians and clinics to women giving birth changed. In Britain and the United States a transition occurred from late to early ambulation. Where some were reluctant to prescribe early ambulation[39-43] others were more progressive.[44-50] Women were no longer regarded as patients, and were restricted less.[13] Babies were allowed to be in the same rooms as their mothers, visitors were welcomed, and women were discharged at an early stage.[13] Many physicians allowed women to move in bed, and gave them a say when to get up. Most women left their bed on the first day to sit in a chair. After this transitional period, most British and American obstetricians were convinced of the negative effects of stasis of the blood on the risk of venous thrombosis and adjusted their policies. In the fifties it was common practice to leave bed on the first or second day after giving birth.

In contrast, in 1953, Mayes in Australia described early ambulation as a controversial, very old idea which had been abandoned years previously.[51] He required women to remain in bed for four or five days, probably because he was afraid that early mobilization would increase the risk of prolapses. Not withstanding this, he thought full ambulation at the earliest reasonable time after confinement was responsible for greatly reducing the morbidity of venous thrombosis.[51]

Some Dutch textbooks, such as that by Amesz published in 1963, still referred to mainly negative effects of early ambulation, such as prolapses and mentioned only a few negative effects after bed rest lasting eight to nine days.[52] However, during this time period more hospitals started implementing early ambulation in daily practice.[53-56] From 1958 onwards, women were advised to get out of bed at an early stage. From the first hours after delivery, women were allowed to move freely. From the second day onwards she was allowed to get out of bed for short periods, while later on women were allowed out of bed for longer periods of time. [53,54,57-60] Binders or elastoplast strapping were less often prescribed and usually bound not as tightly as in the old days.[56,61] From 1973 onwards binders were no longer advised.[55,60] Moreover, deliveries among otherwise healthy women with uncomplicated pregnancies in the Netherlands increasingly took place at home, and it can safely be assumed that all kinds of restrictions will have been somewhat less strict. Therefore, when a woman gave birth at home she would probably not have been in bed for the prescribed period. As only very healthy women gave birth at home, the occurrence of venous thrombosis in this group cannot be compared to that of those who gave birth in the hospital.

Bonnar showed that the number of lethal pulmonary emboli after delivery decreased in England and Wales between 1972 and 1981 compared with the situation in 1952. This was ascribed, among other reasons, to the policy changes regarding early ambulation, since the number of lethal pulmonary emboli during pre-partum period remained stable (figure 1).[7] A similar study by Treffers, also found a remarkable decrease in thromboembolic disease in the post partum period over the years. The main decrease of cases of venous thrombosis was seen in the years 1973 to 1979. However, the early ambulation policy had already been implemented in the late 1950s and early 1960s. Compared to 1952-1957, the 1958-1962

and 1963-1967 periods did not show any decrease in the occurrence of venous thrombosis (figure 1).[62] This led to the conclusion by van Bouwdijk-Bastiaanse that early ambulation did not help in reducing the risk of venous thrombosis.[63] The decrease in the seventies was ascribed to a decreasing age of pregnant women and to the provision of anticoagulant therapy to women who had a caesarean section.[62]

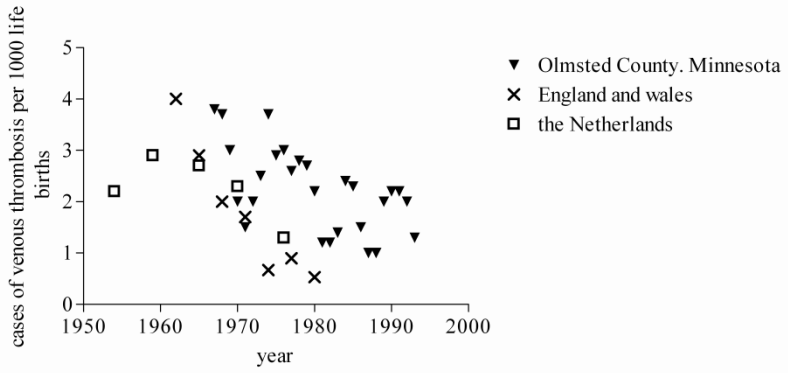

Figure 1. Trends over time for the incidence of venous thrombosis and pulmonary embolism among post partum women in three different countries.26,62,68,69

In Czechoslovakia, Dvorak performed a study in 1977 on the effects of early ambulation after delivery, much like the German obstetricians in the beginning of that century by comparing two time periods. From 1955 to 1964, 9774 women were kept in bed for six weeks. Two percent of them experienced a venous thrombosis: 0.09% a pulmonary embolism, 0.66% a deep venous thrombosis and 1.34% a superficial thrombophlebilis. From 1970 to 1975, 10235 women were mobilised within 24 hours after delivery. No deep vein thrombosis or pulmonary embolisms occurred, while only 0.34% of the women got a thrombophleblitis.[64] However, as with the other studies, no corrections for other changes in practice, like anticoagulation therapy, were taken into account.

1980 - to date

Nowadays it is generally accepted that early mobilisation has mainly advantages. Nevertheless, a number of new studies have been performed over the last few years, since the discussion started whether bedridden pregnant women should be prescribed prophylactic anticoagulants or stasis-reducing treatment. Since it is not justified anymore to keep healthy women in bed after giving birth to a child, most studies on early ambulation are performed with pregnant women who have to remain in bed for diseases or complications.[65] Small increased risks of venous thrombosis of extended bed rest have been found.[65-67] However, similar to studies performed in the beginning of the twentieth century, women who are obligatorily bedridden most often have a lesser health status, which results in a higher risk of venous thrombosis, compared to women who are allowed to leave the bed at an early stage. For this reason, still no accurate risk estimations have been made for comparable groups of women.

Discussion

After Virchow described venous stasis as a risk factor for venous thrombosis, German obstetricians started encouraging women to get out of bed early after childbirth. The first individual promoting this practice was probably Küstner in 1878. He was followed by only a few German obstetricians. However, other countries and obstetricians were reluctant for several reasons, of which fear of prolapses was the most important. Therefore the practice of early ambulation virtually disappeared.

The Second World War and the accompanying baby boom led to a shortage of hospital beds, resulting in a strong practical reason for early ambulation. Early ambulation was implemented in many hospitals. Since no negative effects were found, there was no reason to return to the old practice. After the Second World War a decrease was found in cases of post partum venous thrombosis. However, besides early ambulation, other factors, like anticoagulation and the age of child-bearing women, changed as well. Therefore it is not known whether early ambulation was responsible for this decrease.

We performed an extended literature review and we did not find studies which provided “evidence based proof” according to current standards. As most of the research discussed in

this article was old, mostly performed before the Second World War, it is possible that we may have missed some studies concerning this topic. However, we did check all the relevant references in articles and handbooks. Therefore we believe that if these studies have been performed, their impact was likely to be limited.

Mainly practical reasons, and not profound scientific arguments, were the most important factor in changing the treatment of child bearing women. We do not suggest that more research is needed to study whether extended bed rest is more beneficial than early ambulation as nothing indicates that the former might be better. However, we believe that it is important to note that other factors than evidence based practice have played the major role in the past in shaping the best, currently used, practice.

Acknowledgement

We are in great dept to the (former) obstetricians and gynaecologists who helped us with this project. Prof. Dr H.J. Huisjes and Prof. Dr J.F. Schutte had time for personal interviews and were of great help. Prof. Dr P.E. Treffers and Prof. Dr J. Bennebroek-Gravenhorst also made time for discussions on this topic. We would like to thank J.W. Schoones for helping us with the literature search in the library. We thank Prof. Dr F.R. Rosendaal and Sir I. Chalmers for reading the manuscript carefully.

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Chapter 3

Regular sports activities decrease the risk of venous thrombosis

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Journal of Thrombosis and Haemostasis, 2007 nov; 5: 2186-2192

Abstract

Background: Stasis of the blood has been postulated as a major cause of venous thrombosis. However, little is known about the effect of stimulating the blood flow in order to prevent venous thrombosis through for example sports activities.

Objectives: In a large population-based case-control study (MEGA-study) we studied whether participating in sports activities on a regular basis was associated with venous thrombosis risk.

Patients/Methods: Consecutive patients with a first venous thrombosis of the leg or a pulmonary embolism, and control subjects, consisting of partners of the patients and randomly selected control subjects from the general population, were asked to participate. Sports activities and other risk factors for venous thrombosis were reported in a standardized mailed questionnaire. Participants with malignancy were excluded.

Results: 1136 out of 3608 patients (31.5%) and 1686 out of 4252 control subjects (39.7%) participated in sports activities. Participating in sports activities reduced the risk of venous thrombosis compared with not participating in sports activities (odds ratio (OR) 0.64; 95% confidence interval (CI) 0.58-0.71). Risk reductions were similar after adjustment for sex, age and body mass index (OR_{adj} 0.71; 95% CI 0.64-0.78) and when the analysis was restricted to healthy individuals (OR_{adj} 0.67; 95% CI 0.58-0.78). No differences in risk were found for various frequencies, intensities and types of sport.

Conclusion: Regular sports activities reduce the risk of venous thrombosis.

Introduction

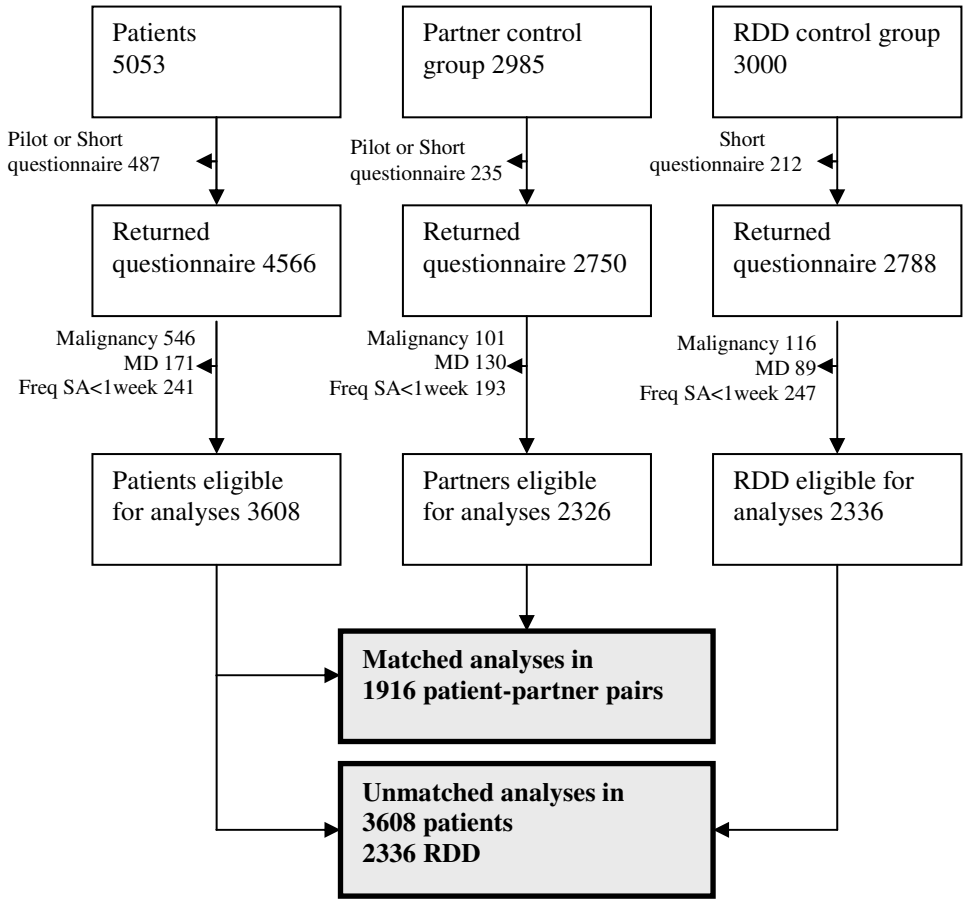
The incidence of a first venous thrombosis is about 1 to 3 per 1000 individuals per year [1,2]. The disorder commonly manifests as a deep vein thrombosis in the legs. Often embolisation occurs resulting in pulmonary embolism which can lead to death in about 1 to 2 percent. Venous thrombosis is a multicausal disease and several risk factors such as malignancy, oral contraceptive use and genetic mutations have been identified [3]. Apart from changes of the composition of the blood and damage of the vessel wall, stasis of the blood has been postulated by Virchow in 1856 as one of the three main causes of thrombosis [4]. Immobilization and physical restrictions are well-known causes of venous thrombosis [5-7]. However, little is known about the effect of stimulation of the blood flow,

i.e. physical activity [8]. In arterial disease, beneficial effects of physical activity have been observed for stroke, cardiac failure and myocardial infarction [9,10]. Furthermore, several studies have shown more beneficial coagulant state in individuals who exercise on a regular basis suggesting a possible beneficial effect on venous thrombosis risk [8,11-15].
We previously showed a beneficial effect of sports activities involving the legs on the risk of venous thrombosis of the arm [16], and one case-control study noted a reduced risk of venous thrombosis of the leg and pulmonary embolisms in young women [17]. On the other hand, two follow-up studies observed that participating in sports activities was associated with a small increased venous thrombosis risk [18,19]. However, in all studies data regarding type, frequency and intensity of sport were scarce, and numbers of venous thrombosis events were small. Therefore, in this study, we set out to investigate in detail whether participating in sports activities on a regular basis influences the risk of venous thrombosis.

Patients and Methods

All analyses were performed as part of the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA-study), which is a large population-based case-control study. Since March 1999 until September 2004, all consecutive patients with a first venous thrombosis were recruited from six anticoagulation clinics in the Netherlands.

These clinics monitor the anticoagulant treatment of all patients within a well-defined geographical area. All patients were between 18 and 70 years of age and had their first episode of venous thrombosis in the deep veins of the leg or had a pulmonary embolism. A participant was considered ineligible when he could not read Dutch or had severe psychiatric problems. 280 Patients died before they were able to fill in a questionnaire (see below) while 82 patients were at the end stage of disease. Out of the remaining 5969 eligible patients, 5053 (84.6%) participated.



MD = missing data regarding sports activities, frequency of sports activities or body mass index
Freq SA<1 week = frequency of sports activities of less than once a week
RDD = random digit dialing controls subjects

Figure 1 Flow chart of participating patients and control subjects for inclusion in the analyses.

Partners of the participating patients were asked to serve as a control group. Those with a history of venous thrombosis were excluded. Of the participating patients, 3657 had an eligible partner of whom 2985 participated (81.6%). A second control group was collected in the same geographical area as the patients via random digit dialing, a method developed by Waksberg [20]. This method is frequently used to gather a random control group. A specific individual from the telephoned household, based on sex and age-range of the patient group, was asked to participate to avoid a selective response from healthy control subjects. In this way it was possible to obtain a random control group frequency matched for age and sex to the patients. Of the 4350 contacted eligible individuals 3000 (69%) were willing to participate. Collection of the random control group started in January 2002 and continued until December 2004. All eligible control subjects were between 18 and 70 years at time of their first contact.

Participants gave a written informed consent. This study was approved by the Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

Data collection

Sports activities, frequency of performing sports, weight, standing height, surgery, plaster cast, minor injury, pregnancy, malignancy, bed rest for more than 4 consecutive days, chronic illness, hormone use and other risk factors for venous thrombosis covering a period of one year prior to the indexdate were reported in a standardized mailed questionnaire. The indexdate was the date of diagnosis of the thrombotic event for the patients and the date of filling in the questionnaire for the control subjects. Body mass index (BMI) was calculated by self-reported weight (kg) divided by height squared $(m)^2$. Minor injuries, such as sprains and small muscle ruptures, had to occur within the three months prior to indexdate. During the first months of the study, a pilot questionnaire was used. When the participant was unable to fill in the questionnaire questions were asked by phone using a standardized short version. As neither of those questionnaires contained information on regular sports activities, these individuals were excluded from the present analysis, figure 1.

Individuals who participated in sports activities at least once a week were considered to exercise. Those who participated in sports activities but with an unreported frequency or with a frequency of less than once a week were excluded, figure 1. A person was considered not to exercise when the activity he performed was not considered a sport activity. Six investigators independently scored whether an activity mentioned in the questionnaire could be considered a sport activity. An activity was considered a sports activity when it was scored as such by three or more investigators. For instance gardening, walking (not for exercise) and bowling were not considered sports activities. Activities were categorized in three different types of sport; endurance, interval, and power sports. The intensity of a specific sport was categorized according to metabolic intensity scores (METS) [21,22] into very strenuous intensity (METS≥ 8), strenuous intensity (METS≥ 6 - 8), and moderate intensity (METS≥ 3 - 6). To study whether the effect of performing sports activities had a local or systemic effect, sports activities were divided into arm and other sports. Bodybuilding, canoeing, climbing, judo, push-ups, rowing, swimming and wrestling were considered as sports mainly involving the arm, so called arm-sports. Other sports activities were categorized as other sports. We further made a distinction between gravitational sports versus non-gravitational sports. Football, volleyball, hockey, athletics, karate, Tai Kwando were considered gravitational sports, while swimming, waterpolo, hydrotherapy, aqua jogging, aqua aerobics and scuba diving were considered non-gravitational sports. Finally, based on the reported incidence density of number injuries per 1000 hours of sports activities[23], sports activities that have a high risk of injuries (more than two injuries per 1000 hours of football, volleyball, hockey, basketball, athletics, karate or Tai Kwando) were compared with sports activities with a low risk of injuries (less than one injury per 1000 hours of fitness, horse riding, swimming or aerobics).

Analysis

Odds ratios (OR) were calculated as estimates of the relative risk of thrombosis with 95% confidence intervals (CI). Odds ratios (OR_{adj}) were adjusted for sex, age and body mass index. Partners were matched to their patients to adjust for lifestyle factors resulting in 1916 eligible couples in a matched analysis (Mantel-Haenszel estimator), while all 3608 patients were contrasted to the random digit dialing controls (2336 subjects) in an unmatched

analysis, figure 1. For calculation of the overall risk we calculated a pooled odds ratio combining the odds ratio of the matched analysis with the odds ratio of the unmatched analysis. This included an adjustment for the patients who were included in both the matched and the unmatched analysis. When analyzing the risk in men and women separately only random control subjects were used, as in most couples partners were of opposite sex. Absolute risk differences were calculated using absolute risks as previously reported in a prospective study on the incidence of venous thrombosis in France [2].

To remove confounding by health status as much as possible, all participants with a malignancy were excluded, figure 1. Furthermore, we performed an analysis for the risk of idiopathic thrombosis in which only individuals were included without clinical risk factors, e.g. surgery, plaster cast, minor injury, pregnancy, malignancy, bed rest for more than 4 consecutive days or chronic illness in the year prior to indexdate. A multivariate analysis was performed among those who participated in sports activities regularly to determine whether type, frequency and intensity of sports activities were independently related to venous thrombotic risk. All analyses were performed in SAS 9.1 (SAS institute Inc, Cary, NC, USA).

Table 1. Characteristics of study population

	Patients N=3608	Control subjects N=4252
Women (%)	54.4%	53.3%
Age (5^{th} -95^{th} perc.)	47.6 (25.6-67.3)	46.6 (25.3-66.4)
BMI (kg/m^2) (5^{th} -95^{th} perc.)	27.0 (20.3-35.9)	25.5 (19.8-33.3)
Type of VT†		
PE (%)	1044 (28.9%)	
DVT leg (%)	2093 (58.0%)	
DVT leg + PE (%)	471 (13.1%)	

† PE = pulmonary embolism
DVT leg = deep venous thrombosis of the leg

Results

Overall 3608 patients and 4252 control subjects were included in the present analysis. Their characteristics are shown in table 1. Of the patients 1136 (31.4%) participated regularly in sports compared with 1686 (39.6%) control subjects. Performing sports reduced the risk of venous thrombosis (OR 0.64; 95% CI 0.58-0.71). Adjustment for sex, age and body mass index did marginally change the odds ratio (OR_{adj} 0.71; 95% CI 0.64-0.78) (table 2). The odds ratios were slightly closer to one when the partner control group was used (OR_{adj} 0.86; 95% CI 0.71-1.02) compared with using the random digit dialing control group (OR_{adj} 0.67; 95% CI 0.60-0.75).

Among participants without an injury in the preceding three months the risk of venous thrombosis was 0.7 fold decreased (OR_{adj} 0.66; 95% CI 0.59-0.74) for those who participated in sports activities compared with those who did not participate in sports activities. When the analysis was restricted to idiopathic thrombosis i.e. individuals without clinical risk factors for venous thrombosis the risk reduction was similar to the overall risk (OR_{adj} 0.67; 95% CI 0.58-0.78). Further exclusion of women receiving oral contraceptives or hormone replacement therapy did not lead to a different point estimate (OR_{adj} 0.66; 95% CI 0.54-0.79).

Table 2. Association between participating in sports activities and the risk of venous thrombosis

	Patients	Control subjects	OR (95%CI)	OR_{adj}^{*} (95%CI)
No sport	2472 (68.6%)	2566 (60.3%)	1	1
Sports	1136 (31.4%)	1686 (39.7%)	0.64 (0.58-0.71)	0.71 (0.64-0.78)
Total	3608	4252		

*Adjusted for sex, age and body mass index
OR = odds ratio
95 % CI= 95 percent confidence interval

Among those participating regularly in sports activities, the frequency of performing a sport did not affect the risk of venous thrombosis. Different types and intensities of sports were equally beneficial (table 3).

Table 3. Relation between frequency, intensity and type of sports activities and risk of venous thrombosis

	Patients 3608	Control subjects 4252	OR_{adj}* (CI95)
No sport	2472	2566	1
Frequency			
Once per week	613	916	0.68 (0.60-0.78)
> Once per week	523	764	0.73 (0.64-0.84)
Intensity†			
Moderate intensity	374	580	0.69 (0.59-0.81)
Strenuous intensity	424	569	0.77 (0.66-0.89)
Very Strenuous intensity	334	531	0.66 (0.56-0.76)
Type of sport†			
Single type of sport(s)	808	1167	0.72 (0.64-0.81)
Only endurance sport(s)	*431*	*585*	*0.78 (0.67-0.90)*
Only interval sport(s)	*194*	*295*	*0.71 (0.58-0.87)*
Only power sport(s)	*183*	*287*	*0.62 (0.51-0.76)*
Combinations of types of sport(s)	324	513	0.67 (0.57-0.78)
Endurance and interval sport(s)	*133*	*208*	*0.73 (0.57-0.92)*
Endurance and power sport(s)	*130*	*1412*	*0.60 (0.47-0.76)*
Interval and power sport(s)	*28*	*51*	*0.58 (0.36-0.93)*
Endurance and interval and power sport(s)	*33*	*42*	*0.85 (0.52-1.36)*

*Adjusted for sex, age and body mass index.

Among those who participated in sports activities, multivariate analysis showed that frequency, intensity and type of sport were not independent determinants of venous thrombosis risk. When we compared the effect of sports that involve mainly the arm with those mainly involving the legs, we found no clear differences on the risk of deep venous thrombosis, with relative risks of 0.79 for arm sports (ORadj 0.79 95%CI 0.66-0.95) and 0.68 for other sports (ORadj 0.68 95%CI 0.61-0.76), both relative to those who did not participate in sports. Non-gravitational sports activities (0.90 95%CI 0.60-1.17) seemed to reduce the risk of venous thrombosis to a lesser extent than gravitational sports activities (0.72 95%CI 0.59-0.88) both compared with performing no sports activities. Furthermore, sports activities that had a high injury risk had a less beneficial effect on thrombotic risk (0.93 95%CI 0.69-1.26) than sports activities with a low injury risk (OR 0.70 95%CI 0.60-0.81) both compared with performing no sports activities.

Those who engaged in sports, compared with those who did not, had a 46 % reduced risk of pulmonary embolism (OR 0.54; 95% CI 0.46-0.64) and only a 24% reduced risk of deep venous thrombosis of the leg (OR 0.76; 95% CI 0.67-0.86). However, only 29% of the venous thrombosis events were isolated pulmonary embolisms, while 58% was located in the leg. When using a venous thrombosis incidence of 1.3 per 1000 person years [2], the absolute risk differences are estimated to be equal for pulmonary embolism and thrombosis of the leg (table 4).

Table 4. Relation between sport (≥ once per week) and risk of different types of venous thrombosis

	Sport		Odds ratio* (95% CI)	Absolute risk		Absolute risk difference
	yes	no		Sport	No sport	
Control subjects	1563	2566	1 (ref)			
PE†	287	757	0.54 (0.46-0.64)	0.25/1000	0.44/1000	0.20/1000
DVT leg†	696	1397	0.76 (0.67-0.86)	0.63/1000	0.83/1000	0.20/1000
DVT leg† + PE†	153	318	0.79 (0.63-0.98)	0.15/1000	0.19/1000	0.04/1000

*Adjusted for sex, age and body mass index

The effect of performing sports seemed slightly different in men and women. In men the risk reduction was 22% (OR_{adj} 0.78; 95% CI 0.66-0.93), while the 39% risk reduction was more pronounced in women (OR_{adj} 0.61; 95% CI 0.52-0.70). Exclusion of women receiving oral contraceptives, hormone replacement therapy and those who were pregnant led to a risk reduction of 55% (OR_{adj} 0.45; 95% CI 0.36-0.57). No differences in odds ratios were found for the different age groups; participants aged 18-39 had an OR_{adj} of 0.71 (95% CI 0.59-0.86), those aged 40-59 had an OR_{adj} of 0.70 (95% CI 0.61-0.81) and those between 60 and 70 years had an OR_{adj} of 0.68 (95% CI 0.52-0.89), all odds ratios compared with those who did not engage in sports. As the risk of venous thrombosis increases with age [2], the absolute risk reduction of venous thrombosis associated with sports activities was higher in old compared with young individuals. For example, if all elderly individuals would exercise, approximately 1.9 per 1000 individuals would get a venous thrombosis on a yearly basis while if all individuals in this age group would not exercise this number would be 2.8 per 1000 individuals per years. As these numbers are 0.2 per 1000 and 0.3 for those aged 18 to 39, the risk benefit that could be obtained in the elderly would be much larger (figure 2).

High body mass index (BMI) increases the risk of venous thrombosis and is associated with a lower participation in sports activities; therefore the effect of both was studied simultaneously. Compared with those who did participate in sports activities and were lean (BMI <25 kg/m^2) lean individuals who did not participate in sports activities had a 1.7-fold increased venous thrombosis risk (OR_{adj} 1.71 95% CI 1.46-1.99). Among those participating in sports activities, being obese (BMI > 30 kg/m^2) resulted in a 3.3-fold (OR_{adj} 3.26 95% CI 2.42-4.39) increased risk compared with being lean (BMI < 25 kg/m^2). Obese participants who did not participate in sports activities had a 4.2-fold increased risk relative to lean individuals who participated in sports activities (OR_{adj} 4.21 95% CI 3.44-5.16).

Discussion

Individuals who participate in sports activities on a regular basis have a lower risk of developing a deep venous thrombosis of the leg and pulmonary embolism compared with those who do not participate in sports activities. Risk reductions were similar in various types, frequencies and intensities of sports.

In a joint database of two large cohort studies, i.e. the Atherosclerosis' Risk In Community (ARIC) and the Cardiovascular Health Study (CHS) a small increased risk to a null effect was found for the association of physical activity and venous thrombosis risk [19]. The analysis was based on 215 individuals who developed their first venous thrombotic event during follow-up, which might have been too few to observe an effect. Another cohort study, the Physicians Health Study with 358 venous thrombosis events, also showed a small increased risk of venous thrombosis with increasing frequency of exercise compared with those who did not exercise at all. Both studies did not provide an explanation for this increased risk. In contrast, as in our study, a case-control study including 196 patients showed a decreased venous thrombosis risk for young physical active women [17]. A difference between these cohort studies and the case-control studies is that in case-control studies patients reported their prior sports activities shortly after the venous thrombotic event. In the follow-up studies, leisure time physical activity data were assessed at baseline. As the median follow-up time was eight to thirteen years, physical activity at baseline may not have accurately reflected physical activity prior to the event. Secondly, both cohort studies studied the risk mainly among the elderly as most patients were over 65 years of age when they had their venous thrombosis. Both case-control studies included individuals with a mean age of 48 and 35 years, resulting in a more than 20 year age difference for the cohort and case-control studies. A third reason for this difference between the results obtained in the case-control and cohort studies might be recall bias, since in case-control studies participants are interviewed after the event. Since cases and partner controls filled in the questionnaire simultaneously, we do not believe recall bias very likely.

We found slight differences between the analyses which only included the partners of cases and which only included the random digit controls. Couples often have similar lifestyles and therefore similar sports activities. We performed a matched analysis that takes this association into account. As this matched analysis also accounts for other, unmeasured, confounders, this might explain why this risk estimates was closer to one compared with the unmatched analysis using the random digit dialing control subjects. However, it is important to note that both analyses yielded beneficial effects of sports activities. Population studies on sports activities in the Netherlands showed that between 48 and 52%

of the population performs one or more sports regularly [24]. This is equal to the percentage in our random control group (44%).

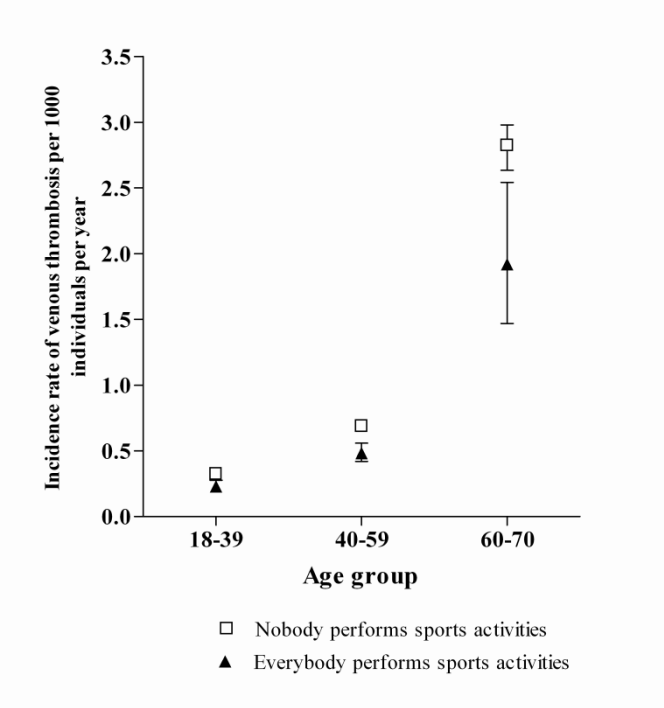


Figure 2 Theoretical number of new cases of venous thrombosis per year if all participants would or would not participate in sports activities

Previously we reported that sports activities involving the legs reduced the risk of venous thrombosis of the arm (systemic effect), whereas sports activities involving the arms increased the risk of venous thrombosis in the arms, which was most striking for thrombosis in the right arm, which most often is the dominant arm used in sports. This suggests systemic and local effects, probably due to a compression of the arm veins [16]. Such differences were not clear for deep vein thrombosis of the leg. A systemic reduction in venous thrombosis risk could be caused by alterations in plasma coagulation factors. Although not all studies have shown to be consistent, decreased levels of both fibrinogen and factor VIII after exercise have been observed [11-14,25]. High levels of fibrinogen, and factor VIII have been shown to increase the risk of venous thrombosis [26,27].

We did not find a dose-response relationship between intensity, frequency and duration of sports activities and risk of thrombosis. It may well be that the beneficial effect is conferred by any engagement in sports, and not further influenced by more frequent of intense engagement. It is also possible that minor injuries play a role in offsetting the beneficial effect. Intense and frequent participation in sports activities results in a high risk of injuries [28] and these may cause venous thrombosis [29]. We found some support for this notion, since participation in sports activities with a high injury risk yielded less benefit than sports activities with a low injury risk.

A potential problem when analyzing the association between sport and disease is that the risk reduction, which appears to have been caused by sports activities, may actually be caused by a reduction in weight or body mass index. Although some believe that physical inactivity is a single cause of cardiovascular diseases and not a high body mass index [10,30]. To ensure that our results were independent of the effect of obesity we adjusted all analyses for body mass index. To study whether body mass index and sports activities have a joint effect we performed a multivariate analysis. Our results show that a high body mass index and not participating in sports activities each individually increase the risk of venous thrombosis, and that the combination of obesity with inactivity leads to the highest risk.

Besides possible confounding by body mass index, the health status of an individual might affect both the risk of venous thrombosis and participation in sports activities. We tried to limit confounding by health status as much as possible by excluding all participants with malignancy. Furthermore we performed an analysis for the risk of idiopathic venous thrombosis, thereby excluding all individuals with known risk factors for disease. The estimate obtained in this analysis was not different from the overall estimate. Although residual confounding by health status might be present, the absence of any effect of these restricted analyses makes us confident that the observed relation between sporting activities and venous thrombosis is causal.

Overall, participating in sports activities on a regular basis decreases the risk of venous thrombosis. All the various types, intensities and frequencies of sports activities decrease the risk to a similar level.

Acknowledgement

The authors wish to thank the directors of the Anticoagulation Clinics of Amersfoort (Dr M.H.H. Kramer), Amsterdam (Dr M. Remkes), Leiden (Dr F.J.M. van der Meer), The Hague (Dr E. van Meegen), Rotterdam (Dr A.A.H. Kasbergen) and Utrecht (Dr J. de Vries-Goldschmeding) who made the recruitment of patients possible. Ms I. de Jonge, Ms R. Roelofsen, Ms M. Streevelaar, Ms L.M.J. Timmers and Ms J.J. Schreijer are thanked for their secretarial and administrative support and data management. The fellows Ms I.D. Bezemer, Ms J.W. Blom, MD, Ms A. van Hylckama Vlieg, PhD, Ms E.R. Pomp, and Ms L.W. Tick, MD took part in every step of the data collection. We express our gratitude to all individuals who participated in the MEGA study. This research was supported by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992) and the Netherlands Organisation for Scientific Research (912-03-033| 2003). The funding organizations did not play a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

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Chapter 4

The relationship between exercise and risk of venous thrombosis in elderly people

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Journal of the American Geriatrics Society. Accepted for publication.

Abstract

Objectives: To study whether exercise is associated with the risk of venous thrombosis in elderly people.

Design: Observational study with a median follow-up of 11.6 years.

Setting: The Cardiovascular Health Study in four U.S. communities.

Participants: People aged 65 and older without prior venous thrombosis (deep venous thrombosis or pulmonary embolism).

Measurements: Self-reported exercise was measured two or three times during follow-up and was defined as expending more than 500 kcal/wk on exercise, including walking for exercise. Venous thrombosis cases were verified using medical record review.

Results: Out of 5534 participants 171 developed a first venous thrombosis. Self-reported exercise at baseline was not related to the risk of venous thrombosis after adjustment for sex, age, race, self-reported health, and body mass index (adjusted hazard ratio (HR_{adj})=1.16, 95% confidence interval (CI)=0.84–1.61), although with exercise modeled as a time-varying exposure, overall results were in the direction of greater risk of venous thrombosis (HR_{adj}=1.38, 95% CI=0.99–1.91). For mild-intensity exercise, such as walking, there was a nonsignificant finding in the direction of benefit (HR_{adj}=0.75, 95% CI=0.49–1.16), but strenuous exercise, such as jogging, was associated with greater risk of venous thrombosis (HR_{adj}=1.75, 95% CI=1.08–2.83) than no exercise at all.

Conclusion: In elderly people, strenuous exercise was associated with a higher risk of venous thrombosis than no exercise at all. Future studies are needed to explain this unexpected higher risk.

Introduction

The incidence of venous thrombosis is 1 to 3 per 1,000 individuals per year. Rates increase with age, and the incidence is as high as 10 per 1,000 per year in elderly people.[1,2] Virchow postulated in 1856 that stasis of the blood was a major contributor to venous thrombosis,[3] and risks are greater in people who are temporarily immobilized or physically restrained.[4,5] For this reason, physical exercise might be expected to lower the risk of venous thrombosis, but little information is available about the association of exercise and venous thrombosis risk.

The Longitudinal Investigation of Thromboembolism Etiology (LITE) study combined data from two large cohort studies (the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk In Communities (ARIC) Study) to investigate risk factors for venous thrombosis in people aged 45 to 100. Previously, an analysis in both cohorts reported no association to a slightly greater risk when studying leisure time physical activity and the risk of venous thrombosis.[6] In the Physicians' Health Study, exercise measured at baseline was associated with greater risk of venous thrombosis during the subsequent 21 years of follow-up.[7] By contrast, in a large population-based case-control study from the Netherlands (the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) Study) of participants aged 18 to 70, moderate and strenuous exercise were associated with lower risk of venous thrombosis in the upper[8] and lower extremities[9] than no exercise. Associations were similar in participants aged 60 and older and those younger than 60. A second case-control study in women aged 15 to 44 who were members of the Kaiser Permanente Medical Care Program also showed that vigorous-intensity exercise resulted in a risk of venous thrombosis of up to 50% less than no physical activity.[10]

Because the results from these observational studies regarding exercise and the risk of venous thrombosis are inconsistent, more information is needed. Neither the CHS nor the Physicians' Health Study analysis provided a detailed analysis of exercise with careful consideration of confounding and time-varying exercise exposure. To study further whether exercise is associated with the risk of venous thrombosis in elderly people, a detailed analysis was conducted in CHS with 4.5 additional years of follow-up and thus more thrombotic events than in the earlier analysis.[6] The analysis included careful consideration of confounding factors, updated assessment of exercise over time, and consideration of exercise intensity.

Methods

Study Population

During a 12-month period beginning in June 1989, four CHS field centers—located in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania—recruited a total of 5,201 participants who were

aged 65 and older (original cohort). A supplemental minority cohort of 687 African-American participants was recruited in 1992 and 1993 from all CHS communities except Washington County. Each community sample was randomly obtained from the Medicare eligibility lists of the Health Care Financing Administration. Participants were considered eligible for participation whether or not they had a history of cardiovascular disease, but persons who were wheelchair bound or were receiving hospice treatment or radiation therapy or chemotherapy for cancer were excluded. Details of the CHS design and recruitment have been described elsewhere.[11] Of the persons contacted and eligible, 58% were enrolled in the study. Information regarding venous thrombotic events, death, and loss to follow-up were complete through December 2001.[2] Participants with self-reported venous thrombosis before baseline (n=354) were excluded from the present analyses. Institutional review boards at all study centers approved the study protocol, and informed consent was obtained from all participants.

Case Ascertainment

The CHS follow-up involved alternating telephone calls and clinic visits every 6 months. Hospitalizations were identified primarily according to self-report of the participant or proxy and search of Health Care Financing Administration records. For every hospitalization, hospital discharge summaries and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) discharge codes were obtained. As previously published,[2] the CHS coordinating center identified cases of possible venous thrombosis events using the ICD-9-CM and procedure codes. Two physicians separately reviewed hospital records and assigned a venous thrombosis classification. Definite deep vein thrombosis required a positive duplex ultrasound, venogram, or other diagnostic test such as computed tomography. Probable deep vein thrombosis required a positive Doppler ultrasound or impedance plethysmography. Definite pulmonary embolism was based on high-probability ventilation–perfusion imaging classified according to Prospective Investigation of Pulmonary Embolism Diagnosis Study criteria, pulmonary angiogram, computed tomography, or autopsy. Probable and definite venous thrombosis and definite pulmonary embolism were considered together for analysis.[2,6]

Table 1. Prevalence of Various Characteristics by Exercise Status in 5534 Participants

	Sports exercise (>=500 kcal/week) N=2081		No Sports Exercise (<500 kcal /week) N=3453	
	N	%	N	%
Age				
65-69	791	38.0	1144	33.1
70-74	685	32.9	1067	30.9
75-79	386	18.6	738	21.4
80-84	156	7.5	360	10.4
85+	63	3.0	144	4.2
Female, %	984	47.3	2174	63.0
Black, %	221	10.6	656	19.0
Body mass index*				
<25	871	41.9	1287	37.4
25-30	906	43.7	1387	40.3
>= 30	298	14.4	767	22.3
Self-reported health*				
Excellent	382	18.4	386	11.2
Very Good	589	28.4	747	21.7
Good	755	36.3	1300	37.7
Fair	316	15.2	839	24.4
Poor	35	1.7	172	5.0
Education*				
< High school	469	22.6	1147	33.3
High school	557	26.8	966	28.1
> High school	1049	50.6	1329	38.6
Income*				
<$16000	628	32.7	1521	46.7
$16000-$25000	404	21.1	619	19.1
>$25000	887	46.2	1114	34.2
ADL, no impairment*	1995	96.0	3111	90.2
IADL, no impairment*	1736	83.6	2419	70.2
Weight change >4.5 kg in the preceding year				
Loss	236	12.0	447	13.7
Gain	136	6.9	333	10.2
Loss & Gain	118	6.0	243	7.4
No change	1484	75.1	2251	68.9

ADL= activities of daily living; IADL instrumental activities of daily living

* Information was missing regarding body mass index for 18; self-reported health 13, education 17, income 361, ADL 9, IADL 7 and weight change for 295 participants.

Each case was classified as idiopathic or secondary venous thrombosis. An event was considered secondary when it occurred within 90 days after acute medical conditions such as major trauma, surgery, or marked immobility or when it was related to cancer. All other venous thrombotic events were considered idiopathic. Venous thrombotic events that occurred within 12 months before or after a cancer diagnosis were considered to be related to cancer.[2]

Exercise Classification

A trained interviewer assessed exercise, race, self-reported health, weight change, activities of daily living (ADLs) and instrumental activities of daily living (IADLs) during the preceding year, and history of cardiovascular disease or cancer, and weight and standing height were measured.[11] ADLs characterize a person's ability to perform basic self-care activities, and IADLs characterize activities necessary for independent functioning in the community, such as housework and shopping.[12] Questionnaires regarding physical activities were administered at baseline (both cohorts), after 3 years of follow-up (original cohort), after 4 years of follow-up (minority cohort), and after 7 years of follow-up (original cohort).

At each exercise assessment, participants were asked to state which physical activities they had performed in the preceding 2 weeks and to indicate the number of times and duration of exercise in the preceding 2 weeks and the number of months per year that each activity was performed. They were specifically asked about walking for exercise, moderately strenuous household chores, mowing, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, calisthenics, and swimming. Participants could report two additional types of leisure time activities in two open text fields. For walking, the usual pace was asked (strolling, normal, fairly brisk, or brisk). In the present analysis, only sports activities, such as water aerobics, biking, jogging, rowing, and walking for exercise, were included; chores, work activities, and hobbies were excluded.

Average kilocalorie expenditure per week was calculated by multiplying the metabolic equivalent (MET) intensity level for each activity (kcal/min)[13,14] by duration (minutes), frequency (per 2 weeks), and months (per year) of exercise, divided by 24. For walking,

different MET intensity scores were used depending on the reported usual pace. Data were missing at baseline regarding duration of exercise for 1.5%, frequency for 1.6%, and months per year for 3.0% of the participants. Missing data were imputed using single-regression imputation based on type of physical activity, duration of exercise, frequency per week, months per year, sex, age, race, and for walking, pace. Exercise intensity was based on MET intensity levels; activities with a MET intensity level below 4, such as walking, were considered low intensity; 4 to 6, such as gymnastics, moderate; and above 6, such as jogging, strenuous intensity.[6,14]

Statistical Analysis

Incidence rates (IRs), hazard ratios (HRs), and 95% confidence intervals (95% CIs) were calculated using survival analysis with exercise data from baseline and exercise modeled as a time-varying exposure, updated at each subsequent exercise assessment, using Cox regression analysis. The amount of exercise was categorized in three different ways: first as exercise versus no exercise (based on a cutoff of 500 kcal/wk); second, in four categories of exercise intensity (none, mild, moderate, and strenuous); and third, in six groups of kilocalories per week (0, 1–200, 201–500, 501–1,000, 1,001–1,500 and >1,500). All analyses were adjusted for sex, age, race, and body mass index (BMI; kg/m^2) at baseline and self-reported health status to provide adjusted hazard ratios (HR_{adj}). Models including baseline exercise were adjusted for baseline self-reported health, whereas models including exercise as a time-varying exposure were adjusted for self-reported health as time-varying covariate.

Separate analyses were performed for venous thrombosis events that were not related to cancer and for idiopathic venous thrombosis. One analysis was restricted to person-time and venous thrombosis events in the year after assessment of exercise. To assess the sensitivity of the results to competing risks such as death due to causes other than venous thrombosis, the cause-specific hazard model, in which participants who died from causes other than venous thrombosis were censored at the time of death, was compared with the crude incidence model, in which it was assumed that these participants would never have developed venous thrombosis by artificially extending the venous thrombosis-free survival time after death until the end of follow-up.

In addition, separate sensitivity analyses limited to healthy participants were performed. Participant was considered healthy if, at the current and all previous assessments, they reported good, very good, or excellent health status, no limitations in ADLs or IADLs, and no loss or gain of more than 10 pounds (4.5 kg) in any 1-year interval because of illness. Additionally, they were required to have no history of cancer or cardiovascular disease[2,15] at baseline.

Because BMI may be both a confounder and an intermediate variable in the association between exercise and venous thrombosis, all analyses were adjusted only for BMI at baseline. To further address this issue, a marginal structural model analysis was performed that allowed adjustment for the confounding effect but not for the intermediate effect of BMI.[16]

All analyses were performed in Stata/SE for Windows 8.0 (Statacorp, College Station, TX).

Results

Of the 5,888 participants in CHS, 5,534 had no history of venous thrombosis before baseline and were included in the present analysis. During a median of 11.6 years of follow-up, 171 participants developed a first venous thrombosis. At baseline, 2,081 participants (37.6%) expended≥500 kcal/wk or more on exercise (exercise group), and 3,453 participants (62.4%) expended less than 500 kcal (nonexercise group) per week. Participants who exercised were on average younger, more likely to be male and lean, less likely to be black, and had better self-reported health, more education, and higher income than participants who did not exercise .(Table 1).

Exercise at baseline was not associated with risk of venous thrombosis (Table 2). After adjustment for sex, age, race, self-reported health, and BMI at baseline, there was no association between exercise and the risk of venous thrombosis (HR_{adj}=1.16, 95% CI)=0.84–1.61). With exercise modeled as a time-varying exposure, findings were in the direction of higher risk of venous thrombosis associated with exercise (HR_{adj}=1.38, 95% CI=0.99–1.91, Table 2).

Table 2. Risk of Venous Thrombosis in All Subjects (n=5534) and in Healthy Participants (n=1807) in Relation to Sports Exercise at Baseline or with Exercise Modeled as a Time-Varying Exposure.

	Exercise*	Cases of venous thrombosis	Time at risk (person-y)	Incidence rate/1000 person-y	Hazard Ratio (CI§)	Hazard Ratio adjusted for sex, age, and race (CI§)	Hazard ratio adj (CI§)
All Participants							
Baseline	No	104	31675	3.28	1	1	1
	Yes	67	20633	3.25	0.98 (0.72 - 1.34)	1.03 (0.75 – 1.41)	1.16 (0.84 - 1.61)†
Time-varying exposure	No	110	34727	3.17	1	1	1
	Yes	61	17577	3.47	1.12 (0.83 - 1.55)	1.19 (0.86 – 1.64)	1.38 (0.99 - 1.91)‡
Healthy participants #							
Baseline	No	27	10169	2.66	1	1	1
	Yes	24	8605	2.79	1.04 (0.60 - 1.80)	1.10 (0.63 – 1.92)	1.16 (0.66 - 2.04)†
Time-varying exposure	No	11	7803	1.41	1	1	1
	Yes	14	5853	2.39	1.74 (0.79 - 3.83)	1.82 (0.82 – 4.05)	1.99 (0.89 - 4.48)‡

* Exercise: No is <500 kcal/week, Yes is ≥500 kcal/week
§ CI=95 percent confidence interval
† Adjusted for sex, age, race, body mass index at baseline and self-reported health at baseline
‡ Adjusted for sex, age, race, body mass index at baseline and self-reported health as time-varying covariate
# Restricted to no previous or current cancer, no history of cardiovascular disease at baseline, good, very good or excellent self-reported health, no impaired ADL or IADL at the most recent assessment, and no self-reported weight change of >10 lbs. due to illness in the year before the most recent exercise assessment

Further adjustment for income, education, ADLs, IADLs, smoking, and diabetes mellitus did not alter these findings. In an analysis limited to healthy participants (n=1,807), findings with exercise modeled as a time-varying exposure were again in the direction of greater risk (HR_{adj}=1.99, 95% CI=0.89–4.48, Table 2). All further analyses considered exercise as a time-varying exposure. Findings were in the direction of greater risk with exercise for venous thrombosis not related to cancer (n=133 events, HR_{adj}=1.38, 95% CI=0.95–2.00) and idiopathic venous thrombosis (n=65 events, HR_{adj}=1.69, 95% CI=1.00–2.83). Results were similar in groups defined according to age (<75 vs ≥75), BMI (<30 vs ≥30 kg/m^2), sex, race (black vs other races), and self-reported health status (excellent, very good or good vs fair or poor).

Table 3. Relation of Intensity of Exercise at Baseline or as a Time-Varying Exposure with Risk of Venous Thrombosis

Model	Intensity of exercise*	Cases of venous thrombosis	Time at risk (person-y)	Incidence rate /1000 person-y	Hazard ratio adj, with no exercise group as reference group (CI§)	Hazard ratio adj, with mild exercise intensity group as reference group (CI§)
Baseline	No exercise	58	13906	4.17	1 (ref)	
	Mild	37	14823	2.50	0.68 (0.45 - 1.04)†	1 (ref)
	Moderate	51	17393	2.93	0.81 (0.55 - 1.19)†	1.19 (0.78 - 1.83)†
	Strenuous	25	6185	4.04	1.28 (0.79 - 2.09)†	1.90 (1.13 - 3.19)†
Test for trend					p= .737	p= .024
Time-varying exposure	No exercise	63	16644	3.78	1 (ref)	
	Mild	32	13519	2.37	0.75 (0.49 - 1.16)‡	1 (ref)
	Moderate	50	16481	3.03	0.98 (0.67 - 1.43)‡	1.29 (0.83 - 2.02)‡
	Strenuous	26	5654	4.60	1.75 (1.08 - 2.83)‡	2.31 (1.36 - 3.94)‡
Test for trend					p= .121	p= .004

* No exercise= 0 kcal/week, Mild intensity exercise (METS<4) Moderate (METS 4-6), Strenuous (METS>6),

§ CI=95 percent confidence interval

†Adjusted for sex, age, race, body mass index, and self-reported health at baseline

‡Adjusted for sex, age, race, body mass index at baseline, and self-reported health as time-varying covariate

Mild-intensity exercise was associated with a slightly but not significantly lower adjusted risk of venous thrombosis than no exercise at all for exercise at baseline and for the time-varying analysis (Table 3).

In participants who exercised, strenuous-intensity exercise, such as jogging, was associated with greater risk of venous thrombosis than mild-intensity exercise, such as walking (test for trend in the fully adjusted time-varying analysis *P*=.004, Table 3). This trend remained after further adjustment for kilocalorie expenditure (test for trend *P*=.02). When five different categories of kilocalorie expenditure in exercise were studied, risk was slightly but not significantly lower for the two lowest kilocalorie exercise groups (1–200 and 201–500 kcal/wk) than for those who did not exercise at all (0 kcal/wk), whereas for those who

exercised, the risk of venous thrombosis was greater with greater energy expenditure (test for trend in the fully adjusted time-varying analysis *P*=.02).

There were 43 venous thrombotic events that occurred within 1 year after an exercise assessment. Considering only person-time in the year after each exercise assessment, the HR_{adj} for exercise compared with no exercise was 1.46 (95% CI=0.75–2.84), with exercise modeled as a time-varying exposure. When testing the sensitivity of the results to competing risks, it was found that the HR_{adj} of 1.43 (95% CI=1.02–1.98) for the crude incidence model was similar to that of the cause-specific hazard model (HR_{adj}=1.38, 95% CI=0.99–1.91). The HR of the marginal structural model analysis again was in the direction of greater risk of venous thrombosis associated with exercise (HR_{adj}=1.51, 95% CI=1.00–2.26).

Discussion

In this observational study of elderly people, the findings were in the direction of greater venous thrombosis risk associated with exercise expending 500 kcal/wk or more than with less than 500 kcal/wk when exercise was modeled as time-varying exposure. Assessing the spectrum of exercise, participants who performed strenuous exercise or expended more kilocalories had a higher risk of venous thrombosis than those who performed mild-intensity exercise or expended fewer kilocalories.

Previous analysis of the LITE data with less follow-up time and thus fewer venous thrombotic events and an analysis in the Physicians' Health Study suggested that exercise was associated with greater risk of venous thrombosis.[6,7] No possible explanation for this greater risk was given. The current detailed analysis found a more-complex relationship, with a nonsignificantly lower risk of venous thrombosis associated with low-intensity exercise than with no exercise and a higher risk associated with high-intensity exercise. Two case-control studies reported a lower risk of venous thrombosis associated with exercise.[9,10] Participants included in these studies were on average younger than in the cohort studies.

In cohort studies, exercise habits were assessed before the venous thrombosis event, whereas in case-control studies, cases provided exercise information after the diagnosis. Although both case-control studies ascertained exercise habits for the period before the

venous thrombotic event, it remains possible that the case subjects' knowledge of their diagnosis influenced the self-report of exercise.

The present study assessed exercise habits at only two or three time points; therefore, reported exercise might not be representative of the time period just before the venous thrombosis. To address this potential problem, the analysis was restricted to cases of venous thrombosis that occurred within 1 year after an exercise assessment, and similar results were found. Nonetheless, short-term changes in exercise habits just before the venous thrombosis were not captured in this study.

In the present study, exercise was self-reported, and the methods used to estimate exercise intensity and kilocalorie expenditure may not be accurate for each participant across the range of ages and fitness of study participants. Furthermore, only venous thrombosis cases that came to clinical attention were identified; it is possible that some cases were missed, but this is likely to be independent of exercise exposure.

When studying exercise, it is difficult to distinguish the relationship with exercise from effects of other factors that are related to exercise and venous thrombosis, such as general health. By adjusting for self-reported health status and BMI and by restricting the analysis to healthy participants, it was attempted to limit the confounding effects of health status on exercise, but residual confounding may have occurred.

Exercise at high levels may be associated with a higher rate of injuries in elderly people. Injuries are common; the National Center for Injury Prevention and Control estimated that in 2000, 7.5% of people aged 65 and older suffered from an unintentional nonfatal injury.[17] It is well known that greater exercise intensity, frequency, or duration leads to greater risk of injuries than lower levels of exercise.[18] Injuries can lead to decreased physical activity, immobility, and a hypercoagulable state.[19] As a consequence, major injuries are known to increase the risk of venous thrombosis,[20] and a recent analysis in the MEGA study indicated that even minor injuries such as sprains contribute to the occurrence of venous thrombosis.[21] Because the current study found a higher risk of venous thrombosis in subjects who performed strenuous-intensity exercise than in those who performed mild-intensity exercise, and elderly people are at greater risk of falling than younger people, an injury–venous thrombosis hypothesis seems plausible. Unfortunately, information regarding injuries not requiring hospitalization before the venous thrombotic

event was not available, although analysis of the risk for idiopathic venous thrombosis, which excluded events following major trauma, produced results similar to those for all venous thrombosis events.

Several studies, including the CHS, have reported that, in elderly people, exercise is beneficial for longevity and is associated with a lower risk of cardiovascular disease.[22,23] Most studies have shown that moderate- and strenuous-intensity exercise are more beneficial than no exercise at all or mild-intensity exercise. The overall benefits of exercise likely outweigh the possible higher risk of venous thrombosis or injuries, but more research is needed to investigate this unexpected higher risk of venous thrombosis in elderly people associated with strenuous-intensity exercise.

Acknowledgements

The authors thank all the contributors, staff, and participants of the CHS for their valuable contributions, especially Ellen S. O'Meara, PhD.

Conflict of Interest: The Cardiovascular Health Study (CHS) was funded by contracts N01-HC-35129, N01-HC-45133, N01-HC-75150, N01-HC-85079 through N01-HC-85086, N01 HC-15103, N01 HC-55222, and U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org. The LITE study was funded by Grant R01-HL-59367 from the National Heart, Lung and Blood institute. This study was supported by a grant from the Leducq Foundation, Paris, France, for the development of Transatlantic Networks of Excellence in Cardiovascular Research and Netherlands Organization for Scientific Research Grant 912-03-033l2003. The editor in chief has reviewed the conflict of interest checklists provided by the authors and has determined that none of the authors have any financial or any other kind of personal conflicts with this manuscript.

Author Contributions: Karlijn van Stralen, Carine Doggen, Thomas Lumley, and Frits Rosendaal: analysis, interpretation of the data, and preparation of the manuscript. Mary Cushman, Aaron Folsom, Bruce Psaty, David Siscovick, and Susan Heckbert: concept and design, acquisition of subjects and data, analysis, interpretation of data, and preparation of the manuscript.

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Chapter 5

Strenuous sport activities involving the upper extremities increase the risk of venous thrombosis of the arm

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Journal of Thrombosis and Haemostasis, 2005 sep: 3 ; 2110 -2111

Introduction

Upper extremity venous thrombosis comprises about 4 % of all venous thrombosis [1]. Central venous catheters are the most common cause, while other risk factors for venous thrombosis of the arm are similar to those of the leg, for example malignancies and surgery[2]. Upper extremity thrombosis also occurs as the Paget-Schrötter syndrome, which results from overdevelopment of the anterior scalene muscle due to vigorous exercise [1]. This is often referred to as effort-related thrombosis and several case reports have been published of athletes developing arm thrombosis after strenuous arm activities [3]. However, there are no risk estimates from controlled studies. In the present population-based case-control study, we evaluated the risk of developing an upper extremity venous thrombosis after regular sport activities. To determine whether it was indeed a local effect, a distinction was made between sports involving mainly one arm like tennis and those involving two arms like swimming.

Patients and Methods

Consecutive patients with a first venous thrombosis of the arm aged 18 to 70 years were included from March 1999 until September 2003 in a large population-based case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study (MEGA study), which has been described previously [2,4]. In the earlier report, we showed risk estimates for upper extremity venous thrombosis, mainly focusing on central venous catheters and malignancies, which were excluded here. Overall, the response of patients with venous thrombosis of the arm was 99% [2]. In all those patients of whom a letter on applied diagnostic methods could be obtained (70%), the diagnosis was objectively confirmed by ultrasound, contrast venography or computertomography. Control subjects were recruited from the general population within the same geographical area by using a random digit dialing method from January 2002 until October 2003 [5]. The control subjects were frequency-matched on sex and age with patients, and 65.8% of the eligible contacted individuals participated. All participating control subjects received a standardised questionnaire within a few weeks after the moment of inclusion and participating cases within a few weeks after their index date. The index date was defined as the date of venous thrombosis for the patients and as the date of filling in the questionnaire for the control

subjects. All participants gave a written informed consent. This study was approved by the Ethics Committee of the Leiden University Medical Center. Body mass index (BMI) was calculated from self-reported weight (kg) divided by height (m) squared as kg/m^2.
Information on sport activities in the twelve months prior to index date was available for all 110 patients and for 1106 (94.7%) of the participating control subjects. To enlarge the contrast between athletes and inactive individuals, we only included participants who indicated to take part in sport at least once a week, and those who indicated not to engage in sport at all. Hence, those with an unknown sport frequency (0 patients and 7 control subjects) or with a frequency of less then once a week (9 patients and 121 control subjects) were excluded. Therefore, 101 patients and 978 random control subjects remained for the present analyses. Sports were divided into categories: badminton, baseball, handball, squash, tennis, volleyball and waterpolo were considered as strenuous sport activities involving one upper extremity or as single arm-sports, while (acrobatic) climbing, bodybuilding, canoeing, fitness, judo, push-ups, rowing, swimming and wrestling were considered as double arm-sports. All remaining sport activities were categorized as 'other sports', and included, among others, running, soccer and cycle-racing.

Analyses were performed for overall thrombotic risk, and for the risk of an idiopathic thrombosis. 68 Patients and 834 control subjects were considered to be at risk for idiopathic thrombosis, since they did not have a surgery, plaster cast, minor injury, or pregnancy and were not immobilized for at least 14 days in the month prior to their index date. Odds ratios (OR) were calculated as estimates of the relative risk with 95% confidence intervals (CI 95%) constructed according to Woolf [6]. By using multiple logistic regression odds ratios were adjusted for age, sex, and body mass index (OR_{adj}).

Results

Median age of the 101 patients was 39.7 (5^{th} - 95^{th} percentile: 20.6 – 64.2) years, while it was 42.9 (5^{th} - 95^{th} percentile: 20.8-66.5) years for the 978 control subjects. There were 53 women (52.5 %) in the patient group and 524 (53.6 %) in the control group. Median BMI of both groups was similar; 24.5 (5^{th} - 95^{th} percentile: 18.3-33.4) kg/m^2 for the patients and 24.4 (5^{th} - 95^{th} percentile: 19.5-32.5) kg/m^2 for the control subjects.

45 Patients (43.7%) were active in sports compared to 453 (44.9%) control individuals. Overall, athletes had no evidently different risk of developing an upper extremity venous thrombosis than those who did not engage in sports (OR_{adj} 0.86; 95% CI 0.57-1.31). No difference was found for those who performed any kind of arm-sports, compared to those not participating in sports (OR_{adj} 1.03; 95% CI 0.65-1.62). Analysis restricted to idiopathic thrombosis yielded the same result (OR_{adj} 1.08, 95% CI 0.63-1.87). Participation in 'other sports' (sports not involving the arms) appeared to decrease the risk of venous thrombosis of the arm (OR_{adj} 0.56; 95% CI 0.27-1.16) compared to those not involved in any sports. The analysis restricted to idiopathic thrombosis suggested the same result, i.e., a reduced risk of arm thrombosis associated with involvement in sports not specifically involving the arms (OR_{adj} 0.61; 95% CI 0.26-1.41) (Table). Compared to those performing other sports, arm-sports slightly increased the risk of venous thrombosis of the arm (OR_{adj} 1.79, 95% CI 0.75-4.29).

Discussion

We found a difference in risk of developing an idiopathic venous thrombosis in the right and left arm. In non-athletes (left arm: 23 of 37 patients, 62%) and in those performing other sports (left arm: 5 of 7 patients, 71%) venous thrombosis occurred slightly more frequently in the left arm compared to the right arm. However, for those involved in arm-sports, most events occurred in the right arm (left arm: 8 of 24 patients, 33%). Only two out of nine patients (22%) who participated in a single arm-sport had their venous thrombosis located in their left arm. This was six out of fifteen (40%) for those participating in double arm-sports. The risk of a venous thrombosis in the right arm was more than two-fold higher for those participating in arm-sports compared to those who did not sport at all (OR 2.04; 95%CI 0.97-4.33). When split into single and double arm sports the adjusted OR was 2.27 (95% CI 0.88-5.81) for those participating in single arm-sports, while it was 1.89 (95% CI 0.79-4.57) for those participating in double arm-sports. For the left arm the risk of venous thrombosis was similar for those performing single arm-sports (OR_{adj} 0.37; 95% CI 0.09-1.62), double arm-sports (OR_{adj} 0.64; 95% CI 0.25-1.65) and other sports (OR_{adj} 0.65; 95% CI 0.24-1.77), compared to non-athletes (Table).

Table. Risk of developing an idiopathic upper extremity venous thrombosis in the presence of sport activities.

Total	Control subjects	Patients total	OR* (95% CI)	Patients left arm	OR* (95% CI)	Patients right arm	OR* (95% CI)
No sports	453	37	1.00	23	1.00	14	1.00
Arm-sports	257	24	1.08 (0.63-1.87)	8	0.54 (0.24-1.25)	16	2.04 (0.97-4.33)
Single arm-sports	*99*	*9*	*1.07 (0.50-2.31)*	*2*	*0.37 (0.09-1.62)*	*7*	*2.27 (0.88-5.81)*
Double arm-sports	*158*	*15*	*1.09 (0.57-2.07)*	*6*	*0.64 (0.28-1.65)*	*9*	*1.89 (0.79-4.57)*
Other sports	124	7	0.61 (0.26-1.41)	5	0.65 (0.24-1.77)	2	0.50 (0.11-2.26)

*OR (Odds Ratio) adjusted for age, sex and BMI

Sport activities not strenuously involving the arm may decrease the risk of upper extremity venous thrombosis. However, sports activities that involve strenuous arm exercise increase the risk of thrombosis in the right arm two fold, with the most evident effect for single-arm sports. This arm is most likely to be the right arm since this will be the dominant arm in most athletes; unfortunately we had no information of left or right dominance. In non-athletes and in those performing other sports venous thrombosis occurred slightly more often in the left arm. This might be due to anatomic differences since the venous brachiocephalica is located more horizontally on the left side [7].

Acknowledgement

The authors wish to thank the directors of the Anticoagulation Clinics of Amersfoort (M.H.H. Kramer), Amsterdam (M. Remkes), Leiden (F.J.M. van der Meer), The Hague (E. van Meegen), Rotterdam (A.A.H. Kasbergen) and Utrecht (J. de Vries-Goldschmeding) who made the recruitment of patients possible. I. de Jonge, R. Roelofsen, J.J. Schreijer, M. Streevelaar, L.M.J. Timmers and P.T.A. Vis are thanked for their secretarial, administrative support and data management. The fellows I.D. Bezemer, A. van Hylckama Vlieg, E.R. Pomp, and L.W. Tick took part in every step of the data collection. We express our gratitude to all individuals who participated in the MEGA study. This research was

supported by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992) and the Netherlands Organization for Scientific Research (912-03-033/2003). The funding organizations did not play a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

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Chapter 6

Minor injuries as a risk factor for venous thrombosis

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Archives of Internal Medicine. 2008 jan: 168 (1); 21-26.

Abstract

Background: Injuries increase the risk of venous thrombosis. So far, most research has focused on major injuries that are accompanied by other risk factors for VT, such as plaster casts and surgery. We studied the association of venous thrombosis with common minor injuries such as minor sural muscle ruptures and ankle sprains.

Methods: We performed a large population-based case-control study (the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis [MEGA] study) including consecutive patients with a first deep venous thrombosis of the leg or pulmonary embolism and control subjects. Participants with malignant neoplasms, those who underwent surgery and those who had a plaster cast, or extended bed rest were excluded.

Results: Of 2471 patients 289 (11.7%) and of 3534 control subjects 154 (4.4%) had a minor injury in the 3 months preceding the venous thrombosis (patients) or completion of the questionnaire (controls). Venous thrombosis was associated with previous minor injury (odds ratio adjusted for sex and age (OR_{adj}) 3.1; 95% confidence interval (CI) 2.5-3.8) compared with those without any injury. The association was strongest for injuries that occurred in the 4 weeks before thrombosis and was not apparent before 10 weeks. Thrombosis was more strongly associated with minor injuries located in the leg (odds ratio adjusted for age and sex 5.1; 95% confidence interval 3.9-6.7), while those located in other body parts were not associated. A fifty-fold increased risk was found in factor V Leiden carriers with a leg injury compared with non-carriers without injury (OR 49.7 95%CI 6.8-362.7).

Conclusions: Minor injuries in the leg are associated with a greater risk of venous thrombosis. Because minor injuries are common, they could be major contributors to the occurrence of VT.

Introduction

Venous thrombosis is a multicausal disease affecting 1 to 3 per 1000 individuals each year [1;2]. Known risk factors are, among others, surgery, immobility, and several prothrombotic genetic variants [3]. So far, studies have focused on major injuries in hospitalised or deceased individuals and were found to be major risk factors for venous thrombosis [4-11]. However, apart from the injury itself, other risk factors for venous thrombosis will be present because of the major injury, such as surgery, plaster cast, hospitalisation and extended bed rest. The risk of so-called minor injuries that do not lead to these additional factors is unknown.

We set up a large population-based case-control study into the cause of venous thrombosis, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study). The present study had 4 main objectives; (1) to estimate the relative risk of venous thrombosis after a minor injury; (2) to investigate characteristics of minor injuries that contribute most to this risk such as location and type of injury; (3) to estimate the relative risk of venous thrombosis of common injuries; and (4) to identify high risk patients by assessing the joint effect of minor injuries with well known genetic predispositions.

Participants and Methods

Participants

From March 1, 1999, until August 31, 2004, all consecutive patients with a first venous thrombosis were recruited from six anticoagulation clinics in the Netherlands. These clinics monitor the anticoagulant treatment of all patients within a well-defined geographical area. All patients had a first episode of deep venous thrombosis in the leg (DVT) or a pulmonary embolism (PE) between the ages of 18 and 70 years. Of the 6331 eligible patients, 276 patients died before they were able to fill out a questionnaire, while 82 had a very short life expectancy and therefore did not participate in this study. Of the remaining eligible individuals 5051 (84.6%) participated.

Information regarding the diagnostic procedure was obtained via hospital records and family physicians for 4059 patients. A DVT was considered definite when a (Doppler) ultrasound showed the presence of a thrombus in the deep veins. A PE was considered definite when confirmed with a high probability VQ scan, positive spiral CT or angiogram.

A PE was considered probable when the diagnosis was based on a low or intermediate probability VQ scan, inconclusive spiral CT or angiogram. For some patients no information regarding the diagnostic procedure was available while other patients were registered at the anticoagulation clinic with a different or additional diagnosis than the one objectively confirmed. In those patients the diagnosis by which the patient was registered at the anticoagulation clinic was added. For these patients we considered a registered PE as probable and a registered DVT as definite. Only 4958 patients were included in whom the diagnosis was considered definite or probable.

Control subjects were included from 2 sources; (1) by inviting partners of patients (81.6% of the partners participated), and (2) by using a random digit dialing method (68.8% participated) [12]. All participants gave a written informed consent. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

Data collection

In a standardised questionnaire participants reported injuries, surgeries, plaster casts and immobilizations covering the period 1 year prior to the index date, along with sport activities, standing height and weight and family history of venous thrombosis. Body mass index was calculated by dividing weight (kg) by height squared (m^2). The index date was defined as the date of diagnosis of the thrombotic event for the patients and the date of completing the questionnaire for the control subjects. The questionnaire was sent to all participants within a few weeks after registration at the anticoagulation clinic or after we contacted the individuals of the random digit dialling control group. During the first few months of the study, a pilot questionnaire was used which did not contain questions regarding injuries. These 156 patients and 41 control subjects were excluded.

Participants were asked to report the most recent injury prior to the index date in a separate specific question related to minor injuries. The questionnaire listed eight common injuries and included an open text field for other injuries. The injuries were categorized irrespective of patient or control status. Seventeen patients who reported an injury after their venous

thrombotic event were excluded. Only injuries that occurred in the three months before index date were included in the present analysis. Subjects who underwent surgery or had a plaster cast, a hospitalisation or extended bed rest at home for at least four days in the year before the index date were excluded (1631 patients, 1004 control subjects), as were individuals who had ever been diagnosed a having malignant neoplasms before the index date (580 patients, 233 control subjects). An additional 1396 partner controls were excluded because their corresponding patient was excluded for one of the reasons mentioned above.

DNA collection and laboratory analyse

Patients and their partners who were included between March 1, 1999 and May 31, 2002 and the random control group were invited to the anticoagulation clinic for a blood draw. Patients and their partners recruited from June 1, 2002 onwards and participants who were unable or unwilling to come to the anticoagulation clinic were sent buccal swabs to collect DNA. Factor V Leiden and the prothrombin 20210A mutation were measured simultaneously [13].

Statistical analysis

Odds ratios (ORs) were calculated as estimates of the relative risk of thrombosis with 95% confidence intervals (CIs). Odds ratios were adjusted for sex and age (OR_{adj}). Partners were matched to their patients to adjust for lifestyle factors resulting in 1260 eligible couples in a matched analysis, while all 2538 patients were contrasted to the random digit dialing controls (2331 subjects) in an unmatched analysis. For calculation of the overall risk we weighted the odds ratio of the matched analysis with the odds ratio obtained by the unmatched analysis. This included an adjustment for patients included in both matched and unmatched analysis. When analyzing the risk in men and women separately only random control subjects were used, as in most couples partners were of the opposite sexes.

The percentage of injuries per week was calculated by dividing the number of individuals with an injury during a particular week by the total number of individuals who did not have an injury prior to that date. We calculated the proportion of calf veins thrombosis and confidence intervals using the exact method. To assess the joint effect of injuries and the factor V Leiden and prothrombin 20210A mutations, ORs were calculated in the presence

of only one risk factor and in the presence of both risk factors, all relative to those individuals with neither risk factor. We also performed a case-only analysis, which results in a synergy index (SI). A SI of one or more indicates synergy on a multiplicative scale. All analyses were performed in SAS 9.1 (SAS institute Inc, Cary, North Carolina, USA).

Results

Overall 2471 patients and 3534 control subjects were included in the present analysis. Their characteristics are shown in table 1. Control subjects with injuries were slightly more often men (52.6% versus 46.6%) and younger (mean age 44.3 versus 46.9 years) compared with those without injuries (data not shown).

Table 1. Characteristics of study population.

	Patients	Control subjects
	N = 2471	N = 3534
Women, No. (%)	1314 (53.2)	1882 (53.3)
Age (5^{th} -95^{th} percentile)	47.8 (24.9-67.6)	46.2 (24.8-66.5)
BMI (5^{th} -95^{th} percentile) (kg/m^2)	27.0 (20.3-35.4)	25.4 (19.8-33.0)
Type of venous thrombosis		
PE, No. (%)	766 (30.9)	
DVT, No. (%)	1454 (59.1)	
DVT leg + PE, No. (%)	251 (10.0)	

Of the patients, 289 (11.7%) had a minor injury in the three months prior to the index date as did 154 control subjects (4.4%). Injury was associated with venous thrombosis (OR 3.0, 95%CI 2.4-3.6). Adjustment for sex and age did not change this risk estimate (OR_{adj} 3.1, 95%CI 2.5-3.8) nor did further adjustment for sport activities and body mass index (OR_{adj} 3.5, 95%CI 2.8-4.3). Injury in 67 patients and 57 control subjects who did not mention a specific date of the injury and was not associated with venous thrombosis (OR_{adj} 1.2, 95%CI 1.1-1.3). These individuals were excluded from all analyses. Random control subjects had slightly more often injuries (4.8 %) than partner controls (3.6%) in the three

months prior to the index date, resulting in slightly different estimated, the OR_{adj} if random controls was 2.8 (95%CI 2.3-3.6) and that of partner controls was 4.2 (95%CI 2.9-6.0).

Thrombosis was more strongly associated with injuries that occurred during the previous 4 weeks (OR_{adj} 4.0, 95%CI 2.8-5.9) than with less recent injuries (figure). Among the patients most injuries occurred in the two to three weeks before the venous thrombosis diagnosis, while fewer events happened in the week directly prior to the venous thrombosis.

In the three month time window, ORs for minor injuries were similar in men (OR_{adj} 3.0, 95%CI 2.1-4.1) and women (OR_{adj} 3.0, 95%CI 2.2-4.2) as were ORs for the young vs old; young, aged 18 to 39 years (OR_{adj} 3.3, 95%CI 2.3-4.6), middle aged 40 to 59 (OR_{adj} 3.1, 95%CI 2.3-4.2) and elderly, aged over 60 (OR_{adj} 3.3, 95%CI 1.5-7.4).

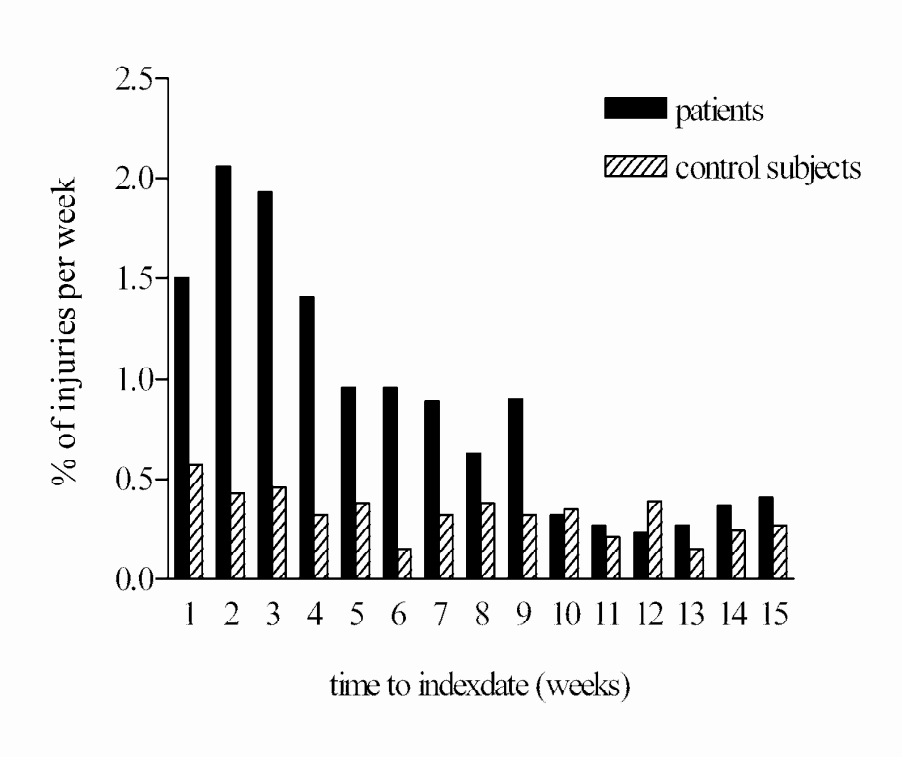

Figure. Percentage of injuries per week before the index date, which was the diagnosis of venous thrombosis (in patients) or completion of the questionnaire (in control subjects). The time window of the analysis concerned the first 13 weeks.

Location of injury

Of the 289 patients with a minor injury, 237 had their injury located in the leg (82.0%), compared with 78 out of 154 injuries among control subjects (50.6%). Therefore, thrombosis was more strongly associated with injury in the leg than with injury located in other body parts Individuals with an injury in the leg were therefore associated with a five-fold greater risk (overall OR_{adj} 1.1, 95%CI 0.8-1.6), table 2.

Table 2. Location of injury and the risk of venous thrombosis

Location injury	Patients	Control Subjects	Odd Ratio*
	2471	3434	(95%CI)
No Injury	2182	3380	1[#]
Leg	237	78	5.1 (3.9-6.7)
Arm	23	43	0.8 (0.5-1.4)
Trunk	14	24	0.9 (0.5-1.9)
Head	1	4	0.3 (0.0-2.4)
Unknown	14	5	3.0 (1.1-8.3)

*adjusted for sex and age - [#] reference group

Injuries in the leg were mainly associated with greater relative risk of an isolated DVT (OR_{adj} 6.3, 95%CI 4.7-8.5). The risk of an isolated PE (OR_{adj} 2.4, 95%CI 1.6-3.7) or a combination of PE and DVT (OR_{adj} 5.3, 95%CI 3.2-8.7) was also greater. For 1101 patients with a DVT, information was available regarding the location of the thrombus. Patients with a leg injury more often had a DVT in isolated calf veins (26.3%, 95%CI 18.9-33.6) compared with patients without an injury (14.5%, 95%CI 12.3-16.7).

Types of injury

(Partial) ruptures of muscles or ligaments in the leg were more strongly associated with a venous thrombosis than were other injuries such as sprains and contusions. Multiple injuries occurring simultaneously were strongly associated with venous thrombosis, table 3.

Table 3. Type of injury in the leg and risk of venous thrombosis

	Patients	Control subjects	Odds ratio*
	2419	3458	(95%CI)
No Injury	2182	3380	1[#]
Muscle or ligament Rupture	70	11	10.9 (5.6 - 21.3)
Contusion	6	5	2.0 (0.5 - 7.6)
Sprain	77	40	3.1 (2.1 - 4.6)
Multiple types of injury	24	4	9.9 (3.3 - 29.6)
Other	33	8	6.9 (3.1 - 15.0)
Unknown	27	10	4.6 (2.2 - 9.8)

*adjusted for sex and age - [#] reference group

Specific injuries most strongly associated with thrombosis were ruptures of the sural muscle ("tennis legs") and knee ligament ruptures while knee and ankle sprains were associated to a lesser extend with venous thrombosis, table 4.

Table 4. Specific injuries in the leg and their risk of venous thrombosis

Specific injuries	Patients	Control subjects	Odds ratio*
			(95%CI)
No Injury	2182	3380	1[#]
Rupture sural muscle (tennis legs)	56	5	22.5 (8.3 - 61.5)
Rupture knee ligaments	24	6	6.3 (2.6 - 15.0)
Ankle sprain	39	24	2.6 (1.6 - 4.1)
Knee Sprain or meniscus problems	47	16	5.1 (2.9 - 8.9)

*adjusted for sex and age - [#] reference group

Prothrombotic factors

In individuals who indicated having a first degree family member with a history of venous thrombosis, leg injury was associated with an estimated twelve-fold relative risk of venous thrombosis (OR_{adj} 12.0, 95%CI 5.9-24.7) compared with no injury in individuals without a family history. This finding suggests a joint effect with genetic factors. The estimated relative risk in carriers of the factor V Leiden mutation with an injury compared with noncarriers without an injury was almost 50 (table 5).

Table 5. Joint effect of prothrombotic mutations and injuries in the leg.

Prothrombotic mutations	Injuries	Patients 2243	Control subjects 2639	Odds ratio* (95%CI)
Factor V Leiden				
-	-	1623	2388	1[#]
+	-	351	135	5.0 (4.0 - 6.2)
-	+	181	59	6.8 (4.9 - 9.4)
+	+	39	1	49.7 (6.8 – 362.7)
FII 20210a mutation				
-	-	1874	2477	1[#]
+	-	100	46	3.4 (2.3 - 5.0)
-	+	206	55	7.0 (5.1 - 9.6)
+	+	14	2	8.6 (1.9 – 37.9)

*adjusted for sex and age - [#] reference group

Because the number of controls with an injury and the factor V Leiden mutation was low, a SI calculation in only patients was performed. This calculation (SI= (1623*39)/(351*181) = 1.0) suggested a joint effect at a multiplicative level and a thirty-fold (1.0*5.0*6.8=34) relative risk for those having the factor V Leiden mutation and a leg injury compared with those neither having the factor V Leiden mutation nor injuries.

The prothrombin 20210A mutation was associated with a 3-fold estimated relative risk of venous thrombosis among those without an injury (OR_{adj} 3.4, 95%CI 2.3-5.0). When both risk factors were present the estimated relative risk of venous thrombosis was nine-fold (OR_{adj} 8.6, 95%CI 1.9-37.9) compared with individuals without injury and the prothrombin 20210A mutation. The SI calculation (SI= (1874*14)/(206*100)= 1.3) suggested interaction at a multiplicative level and a thirty-fold (1.3*3.5*7.0=30) relative risk for the joint effect of the prothrombin 20210A mutation and leg injuries.

Discussion

Minor injuries that do not require surgery, a plaster cast or extended best rest were associated with a three-fold greater relative risk of venous thrombosis. The association appeared local as injuries in the leg were associated strongly with thrombosis, while injuries in other locations were not associated with venous thrombosis. The association was strongest for injuries that occurred in the month before the venous thrombosis, suggesting a transient effect. The association of venous thrombosis with leg injuries was strong in individuals with a genetic predisposition.

Most studies have focused on major or even fatal injuries. Because these studies were performed in hospitals, individuals who had an injury were also hospitalised and immobilised. Therefore it is difficult to make a distinction between the effect of hospitalisation, surgery, plaster cast, extended bed rest and the effect of injury. In studies that focused on major injuries, an asymptomatic venous thrombosis was detected in 0.4% to 12% of the trauma patients, despite prescribed prophylaxis [7-9;14]. One study found a three-fold increased risk of venous thrombosis after minor events[15]. However, minor events included among others travel, minor surgery and minor trauma and no information regarding minor trauma alone was available. Therefore, the risk of minor injuries could not be abstracted.

We found that the association of venous thrombosis with minor injuries was transient and that the excess risk disappeared after 10 weeks. Surprisingly, more injuries were found in the two to three weeks before the venous thrombosis compared with the week directly before the venous thrombosis. Although the differences were small and chance variation may have occurred, it is likely that this difference is true. It may take time before a clot becomes clinically apparent. However, this seems less probable as venous thromboses rates after air travel were highest in the first week after air travel [16]. More likely, because of the symptoms of the injury itself, the patient and physician may not recognise the venous thrombosis at first as the clinical characteristics are similar.

Injuries were strongly associated with venous thrombosis in individuals with genetic predisposition or a family history of venous thrombosis. We found a 50-fold greater risk in individuals with a factor V Leiden mutation and an injury. Because the risk associated with venous was highest in the first month after the injury and decreased sharply thereafter, we believe that many cases of venous thrombosis could be prevented when high-risk individuals with injuries would receive short-term prophylactic treatment. However, data are scarce and future research is needed to show whether this would be safe.

Several reasons why injuries increase the risk of venous thrombosis are conceivable. In 1856 Virchow described three main risk factors for thrombosis; hypercoagulability, stasis of the blood, and damage of the vessel wall[18]. First, several studies have shown an increased prothrombotic state in severely injured patients [19;20]. However, this increased prothrombotic state was not predictive of venous thrombosis in severely injured patients[20]. Because injuries not located in the leg were not associated with a higher risk of venous thrombosis in our study, we do not believe that a systemic reaction to minor injuries explains the thrombotic risk. Second, immobilisation leading to stasis of the blood could play an important role. To rule out this effect we excluded individuals with extended bed rest or immobilisation due to plaster casts. However, even minor injuries could have lead to reduced mobility, not necessarily bed rest, which could have led to thrombosis. Obstruction of the vein by oedema may have caused stasis as well. Third, damage of the vessel wall due to an injury may lead to a local increased risk of venous thrombosis.

Information on minor injuries was obtained after the thrombotic event. Patients could link their injuries to the thrombosis and therefore report the injury in the questionnaire, whereas control subjects do not have a specific event through which they can remember their injuries and therefore may not remember their injury (recall bias). However, the questionnaire for control subjects covered the period prior to filling it in. As risks were only increased up to 10 weeks, it seems likely that control subjects will have remembered their minor events during this period. A second reason why recall bias seems doubtful is that the risk of pulmonary embolism was also markedly increased and patients probably do not link their leg injury to pulmonary embolism. Referral bias could have occurred if physicians

would be more likely to diagnose or refer an injured patient for venous thrombosis examination. This would lead to an overestimation of the risk of venous thrombosis after injury. One study, also from the Netherlands, could not find a higher risk of being referred for venous thrombosis among women using oral contraceptives[21]. However, we do not know whether this is also true for minor injuries.

Our study showed that 4.4% of the control subjects had suffered a minor injury in the three months prior to indexdate. Since minor injuries are common, they can be responsible for many cases of venous thrombosis, as can be shown by the population attributable fraction. Of the patients 289 out of 2471 (11.7%) patients had a minor injury. The risk of venous thrombosis was three-fold increased, resulting in a population attributable fraction of 7.9% (11.7*(3.1-1)/3.1=7.9). Because other injuries were not associated with venous thrombosis risk, this population attributable fraction was entirely due to injuries in the leg (7.7%). This suggests that minor injuries in the leg may be involved in 8 percent of the venous thrombotic events.

The relative risk of venous thrombosis was estimated after minor injuries that did not require plaster cast, hospitalisation or extended best rest. As minor injuries are common they can be major contributors to the occurrence of venous thrombosis. Many individuals with minor injuries will have contacted the general practitioner first. Therefore, there may be an important task for general practitioners to identify subjects who are at a high risk of developing venous thrombosis, and subsequently to provide prophylactic measures.

Acknowledgement

We thank the directors of the Anticoagulation Clinics of Amersfoort (M.H.H. Kramer, MD), Amsterdam (M. Remkes, MD), Leiden (F.J.M. van der Meer, MD), The Hague (E. van Meegen, MD), Rotterdam (A.A.H. Kasbergen, MD), and Utrecht (J. de Vries-Goldschmeding, MD) who made the recruitment of patients possible. The interviewers (J.C.M. van den Berg, B. Berbee, S. van der Leden, M. Roosen, and E.C. Willems of Brilman) performed the blood draws. We also thank I. de Jonge, MSc, R. Roelofsen, MSc, M. Streevelaar, L.M.J. Timmers, MSc, and J.J. Schreijer for their administrative support

and data management. The fellows I.D. Bezemer, MSc, J.W. Blom, MD, A. van Hylckama Vlieg, PhD, E.R. Pomp, MSc, L.W. Tick, MD took part in every step of the data collection. C.J.M. van Dijk, R. van Eck, J. van der Meijden, P.J. Noordijk, and T. Visser performed the laboratory measurements. H.L. Vos supervised the technical aspects of DNA analysis. We would further like to thank Ms S. le Cessie, the Netherlands for her statistical expertise.

We express our gratitude to all individuals who participated in the MEGA study. This research was supported by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992) and the Netherlands Organisation for Scientific Research (912-03-033| 2003). The funding organizations did not play a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

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Chapter 7

Mechanisms of the factor V Leiden paradox

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Submitted for publication

Abstract

Objective: Carriers of the factor V Leiden mutation (FVL-carriers) have a substantially increased risk of deep venous thrombosis (DVT) while the risk of pulmonary embolism (PE) is only mildly increased compared with non-carriers. So far few studies have investigated possible mechanisms for this so-called FVL paradox.

Methods and Results: Consecutive patients with a first DVT or PE were included in a large population-based case-control study (MEGA study). Patients, aged 18 to 70 years, provided a questionnaire, DNA (n=3313) or plasma (n=1474). Surgery, injury and travel were considered thrombosis-provocative. Out of 2063 patients with isolated DVT 20% was FVL-carrier, as was 8% of the 885 patients with isolated PE. Among DVT patients FVL-carriers had their thrombi more often proximal and a higher number of affected veins than non-carriers. No differences were observed between FVL-carriers and non-carriers in time between provocation and diagnosis, in vitro coagulation time and thrombus density. Compared with patients with both DVT and PE, isolated DVT patients more often had thrombi located distally and had a similar number of affected veins. Compared with isolated PE patients, isolated DVT patients had a shorter time between provocation and diagnosis, and similar in vitro coagulation time and thrombus density.

Conclusion: Although some effects were differential for FVL-carriers and non-carriers, and some were differential for PE and DVT patients, none of the potential mechanisms offered a clear explanation.

Introduction

The incidence of venous thrombosis is about 1 to 3 per 1000 individuals per year and is associated with life-threatening pulmonary embolism (PE)[1]. Both autopsy [2] and clinical [3;4] studies have shown that approximately 90% of the pulmonary emboli arise from thrombi in the deep veins of the lower limbs. Moreover, asymptomatic PE can be found in about half the patients presenting with deep venous thrombosis (DVT) [5]. For this reason many consider DVT and PE as a single disease which is referred to as venous thrombosis or venous thrombosis.

However, several studies have shown that the prevalence of some risk factors differs in patients with DVT compared with those with PE [6-9]. The factor V Leiden mutation, the most prevalent genetic factor known to increase the risk of venous thrombosis, has repeatedly been shown to be a strong risk factor for DVT, but at most a weak risk factor for PE. Shortly after the discovery of the Factor V Leiden mutation, it was hypothesized that the presence of Factor V Leiden would often lead to fatal PE, resulting in a lower number of Factor V Leiden positive subjects among those surviving PE. This would explain the weak effect of Factor V Leiden on the risk of PE found in studies of survivors of venous thrombosis, such as case-control studies. However, this hypothesis was rejected as autopsy studies have shown that among patients with fatal PE, the proportion of individuals with Factor V Leiden was no different from that in PE survivors or from that in the general population [10;11].

The differential effect of Factor V Leiden on DVT and PE is known as the "Factor V Leiden paradox" [13]. Although this paradox has been reported repeatedly [8;12-14], some still doubt whether it exists. We therefore studied the prevalence of Factor V Leiden among patients with an isolated DVT, isolated PE, or a combination of DVT and PE. Furthermore, we studied whether the effect was specific for Factor V Leiden, by assessing the effect of the prothrombin 20210A mutation, another well-known factor involved in the risk of venous thrombosis.

So far, few studies have investigated mechanisms that could lead to the Factor V Leiden paradox, except for a possible difference in thrombus location. In this study, we sought to investigate several potential explanations for the paradox. First we studied the difference in location. Second, we focused on differences in number of affected veins. A third possible mechanism was a difference in time interval between the provocation of thrombus formation and the actual diagnosis. The fourth possible mechanism was a difference in growth speed as expressed by *in vitro* coagulation time. A fifth, related, mechanism was a difference in clot structure with lower chances of thrombus breaking which might be expressed as a difference in *in vitro* clot density.

In this study we investigated these five possible mechanisms by determining a) whether Factor V Leiden affects thrombus location, number of affected veins, time until diagnosis, growth speed or clot density and b) whether these factors differ in prevalence between patients with isolated deep venous thrombosis of the leg compared to patients with isolated pulmonary embolism or combined deep venous thrombosis and pulmonary embolism.

Material and Methods

All analyses were done as part of the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study), a large population-based case-control study. Between March 1999 and September 2004 all consecutive patients with a first episode of venous thrombosis were recruited from six anticoagulation clinics in the Netherlands. These clinics monitor the anticoagulant treatment of all out-patients within a well-defined geographical area. Eligible participants were between 18 and 70 years at time of their inclusion. Patients who died (n=280) and those who were at the end stage of disease (n=82) and were therefore unable to fill in a questionnaire were excluded. Of the 5969 eligible patients, 5051 (84.5%) were willing to participate.

Control subjects were recruited from two sources; first, by inviting partners of patients (82% of the partners participated), and second by using a random digit dialing method (69% of the eligible individuals participated). All participants provided informed consent in which they agreed to participate. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

Data collection

Risk factors for venous thrombosis including surgery, injury and travel were reported in a standardized mailed questionnaire covering a period of one year prior to the venous thrombotic event. The questionnaire included a permission form to obtain information regarding the diagnostic procedure of the thrombotic event from existing medical records. Informed consent to obtain medical records was given by 4528 out of 5051 patients (90%). Diagnostic information regarding the thrombosis was obtained via hospital records or

general practitioners. Only those patients of whom information could be obtained and who had an objectively confirmed DVT or PE were included (n=3574), figure 1.

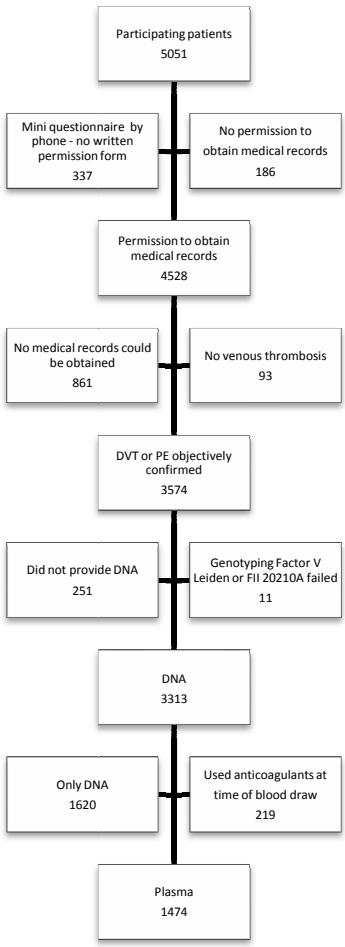

Figure 1. Flowchart of patients.

DVT was considered to be objectively diagnosed when a (Doppler) ultrasound showed the presence of a thrombus in the deep veins of the leg. PE was considered to be objectively confirmed when diagnosed with a high probability ventilation perfusion (VQ) scan, positive spiral computational topography (CT) or angiogram. A patient registered at the anticoagulation clinic with both PE and DVT, but with only one of these diagnoses

objectively confirmed according to the above mentioned criteria, was considered to have both PE and DVT.

We analyzed a subgroup of patients who had at least two diagnostic tests; at least one of the legs and one of the lungs. Patients who had a thrombus in the leg and tested negative for PE were considered to have isolated deep venous thrombosis. Patients with a positive lung scan but tested negative for DVT considered to have isolated PE.

Location of the thrombus and number of affected veins were abstracted from radiology reports and discharge letters without knowledge of the presence or absence of the Factor V Leiden mutation. Information regarding the location of the thrombus in the leg was available for 2083 patients with DVT, but obviously not for patients with an isolated PE. A thrombus in the calf veins only was defined as located distally, whereas a thrombus in any of the other veins was defined as proximal. For calculation of time between the onset of thrombus formation and diagnosis only patients who had surgery, an injury or had traveled in the 100 days prior to the diagnosis of venous thrombosis were included. In these patients we assumed that thrombus formation started shortly after provocation.

DNA collection and laboratory analyses

Patient included between March 1999 and May 2002 were asked to provide a blood sample 3 months after discontinuation of anticoagulant treatment, while those who were unable or unwilling to come to the anticoagulation clinic for a blood draw were sent a cotton swab for the collection of buccal cell DNA. From May 2002 onwards DNA was collected through buccal swab samples only. Assessment of the Factor V Leiden mutation was performed identically in DNA retrieved from whole blood and buccal swabs, as described previously [15]. Individuals who did not provide DNA (251 patients) and samples where genotyping of Factor V Leiden failed (11 patients) were excluded from the present analyses, resulting in a total of 3313 patients who were eligible for analysis, figure 1.

Blood samples were drawn into vacuum tubes containing 0.106 M trisodium citrate as anticoagulant. Fresh frozen plasma was obtained by centrifugation at 2000g for 10 minutes at room temperature and stored in aliquots at -80°C. Coagulation parameters were derived

from clot lysis experiments as described previously[16]. In short, a tissue factor-induced thrombus, which was lysed by exogenous t-PA, was studied by monitoring changes in turbidity during thrombus formation and subsequent lysis by measuring the optical density at 405 nm every 20 seconds. *In vitro* coagulation time was defined as time from adding the buffer till the midpoint of the clear to maximum turbid transition. Thrombus density was defined as the difference in light absorbance between the maximum turbidity minus the minimal turbidity, measured in optical densities (OD). For the calculation of *in vitro* coagulation time and thrombus density only those patients who donated plasma but did not receive anticoagulant treatment at time of blood draw were included in the analysis (n=1474).

Statistical Analyses

Percentages and 95 % confidence intervals (95% CI) were calculated using the exact method. Differences in time between provocation and diagnosis of venous thrombosis were determined using a log-rank test. All analyses were performed in SPSS for windows 14.0 (SPSS Inc, Chicago, Ill).

Results

A total of 3313 patients was included in the present analysis of whom 2063 were objectively diagnosed with DVT, 885 with PE and 365 with both. The characteristics of these three groups and the control subjects are shown in table 1.

Of the patients with DVT, 415 carried the Factor V Leiden mutation (20%), 60 patients with both DVT and PE carried the Factor V Leiden mutation (16%) and 75 patients with PE (8%) carried Factor V Leiden, compared with 256 control subjects (5%). Therefore the risk of DVT was 4.5 fold increased (OR 4.5 95% CI 3.8 to 5.3), while the risk of PE was only mildly increased (OR 1.7 95% CI 1.3 to 2.2) in carriers of Factor V Leiden, both compared with non-carriers.

Table 1. Characteristics of 3313 patients with isolated deep venous thrombosis of the leg (DVT), DVT combined with pulmonary embolism (PE), isolated PE and control subjects.

	DVT	DVT+PE	PE	Controls
N	2063	365	885	4857
Sex, women, N (%)	1093 (53%)	166 (46%)	502 (57%)	2589 (53%)
Age, mean (year)	48.2	50.3	49.1	48.1
Surgery, N (%)	440 (21%)	70 (19%)	210 (24%)	326 (7%)
FVL heterozygous, N(%)	393 (19%)	55 (15%)	71 (8%)	248 (5%)
FVL homozygous, N(%)	16 (1%)	5 (1%)	3 (0%)	8 (0%)
FII carrier, N(%)	121 (6%)	24 (7%)	38 (4%)	94 (2%)

DVT = deep venous thrombosis of the leg, PE = pulmonary embolism
FVL = Factor V Leiden; FII= factor II 20210A

When we studied the subgroup of patients who had had diagnostic tests performed of both lungs and legs, 30% of the patients with isolated DVT carried the Factor V Leiden mutation and only 7% of patients with isolated PE. When comparing these results with the control group, the risk difference was even more pronounced: the risk of isolated DVT for carriers of the Factor V Leiden mutation was almost 8-fold increased (OR 7.7 95% CI 3.9 to 15.3), while Factor V Leiden only mildly affected the risk of isolated PE (OR 1.4 95% CI 0.7 to 2.7), both compared with non-carriers.

This differential effect was specific for Factor V Leiden and not for prothrombin 20210A mutation, which was present in 121 out of 2063 patients with DVT (5.9%) and 38 out of 885 patients with PE (4.3%). Odds ratios for carriers of the prothrombin 20210A mutation were clearly elevated with overlapping confidence intervals for both DVT (OR 3.2 95% CI 2.4 to 4.2) and for PE (OR 2.3 95% CI 1.5 to 3.3).

Location

Differences in Factor V Leiden prevalence between patients with proximal and distal DVT were small. Among those with proximal DVT, 318 out of 1559 (20%) carried the Factor V Leiden mutation while this was 53 out of 329 (16%) patients with distal DVT; difference 4% (95% CI 0 to 9%), table 2. Patients with DVT more often had distally located thrombi (302 out of 1635 patients, 19%) compared with patients with both PE and DVT (27 out of 253 patients, 11%), difference 8% (95% CI 3 to 12%).

Table 2. Percentages of Factor V Leiden carriers in patients with different thrombus locations and number of affected veins.

	FVL	Total	Percentage FVL *(95% CI)
Location †			
Proximal thrombosis ‡	318	1559	20% (18 - 22)
Isolated inferior cava	*1*	*7*	*14% (-14 - 42)*
Isolated iliac vein	*6*	*49*	*12% (4 - 25)*
Iliofemoral vein	*12*	*61*	*20% (11 - 32)*
Isolated femoral vein	*40*	*170*	*24% (17 - 30)*
Popliteal-iliofemoral vein	*11*	*58*	*19% (9 – 29)*
Popliteal-femoral vein	*79*	*356*	*22% (18 - 27)*
Isolated popliteal vein	*169*	*858*	*20% (17 - 22)*
Distal thrombosis			
Isolated calf veins	53	329	16% (12 - 20)
Number of affected veins			
One vein	216	1208	18% (16 - 20)
≥ 2 veins	175	750	23% (20 - 26)

* FVL=Carrier of the Factor V Leiden mutation
† other locations for 70 patients
‡ On occasion combined with a thrombus in the calf veins

Number of affected veins

Of the 755 patients who had multiple veins affected, 175 carried the Factor V Leiden mutation (23%) while this was 216 out of 1208 (18%) patients who had only one vein affected, a difference of 5% (95% CI 2 to 9%), table 2. The number of affected veins was similar in patients who had an isolated DVT as in patients with a combination of DVT and

PE, 650 out 1690 (39%) had 2 or more veins affected while this was 100 out 268 patients who had combination of DVT and PE (38%), a difference of 1% (95% CI -7 to 5 %).

Time interval between provocation and diagnosis

We studied the time interval between Factor V Leiden carriers versus non-carriers in patients who were diagnosed with DVT or PE within the first 100 days after provocation of thrombus formation (n=1048). Within this time window, carriers of the Factor V Leiden mutation had a similar time interval between provocation and the diagnosis as non-carriers ($p>0.05$), figure 2a. Patients with PE were diagnosed slightly longer after provocation compared with patients with DVT ($p<0.05$), figure 2b.

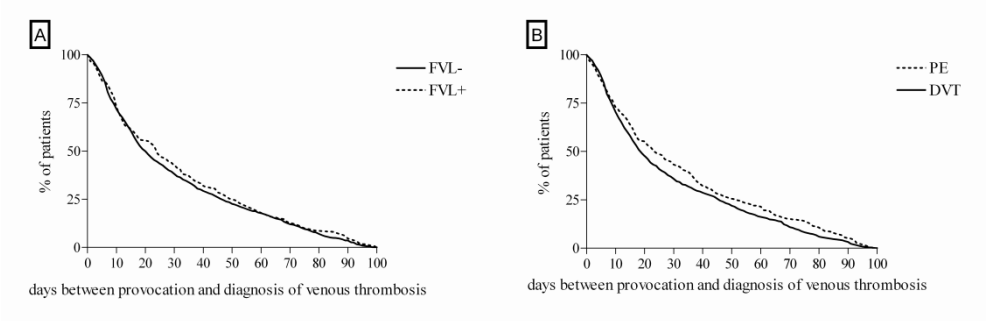

Figure 2. Time interval between provocation and venous thrombosis for Factor V Leiden carriers versus non-carriers (A) and in patients with deep venous thrombosis or pulmonary embolism (B).

In vitro coagulation time

In vitro coagulation time was similar in patients with Factor V Leiden (2.45 minutes) and non-carriers (2.46 minutes), a difference of 0.01 minutes (95% CI -0.07 to 0.08). Also no differences were observed in coagulation time between patients with DVT (2.45 minutes) and PE (2.47 minutes), difference (0.02 minutes 95% CI -0.04 to 0.09).

Thrombus density

Factor V Leiden carriers had a slightly lower thrombus density (mean OD 0.46) compared with non-carriers (mean OD 0.48), difference 0.02 (95% CI 0.01 to 0.04). However, thrombus density was similar in patients with isolated DVT (mean OD 0.47) and isolated PE (mean OD 0.47, difference 0.00 95% CI -0.01 to 0.01).

Discussion

The prevalence of Factor V Leiden is substantially higher in patients with DVT, in presence of absence of a concomitant PE, than in patients with isolated PE. In fact, Factor V Leiden is only a mild risk factor for isolated PE, whereas the risk of DVT is substantially increased by this mutation. We studied multiple explanatory mechanisms for the differential effect of Factor V Leiden on the risk of DVT and PE: thrombus location, number of affected veins, time between provocation and diagnosis, in vitro clot formation and in vitro clot density. Although some effects were different for Factor V Leiden carriers and non-carriers, and some were different for patients with PE and patients with DVT, none of the mechanisms offered a clear explanation.

Location

So far, studies have been inconsistent on whether the thrombus location is different in Factor V Leiden carriers compared with non-carriers. Some studies, including ours, showed that the presence of Factor V Leiden leads to increased risk of thrombosis in the proximal veins [19;20], while others have shown the opposite [17;18;22], or found no difference in location [21;23].

More distal located thrombi are less likely to be accompanied by PE, which is in agreement with other studies [4;24;25]. Therefore, if Factor V Leiden would lead to more distal located thrombi, and proximal located thrombi would lead to PE, one would expect that Factor V Leiden carriers were at lower risk for PE. However, as the results in the literature regarding the location of thrombi in Factor V Leiden carriers are inconsistent, and we even found an increased risk of a proximally located thrombus for Factor V Leiden carriers, it is unlikely that the location of the thrombus in the leg explains the risk difference of Factor V Leiden in DVT and PE risk.

Thrombus size

Murine models have shown that mice homozygous for the Factor V Leiden mutation had a larger thrombus volume compared with wild-type mice[26]. This is in line with our results as we showed that carriers of the Factor V Leiden mutation more often had multiple veins affected compared with non-carriers. It seems logical that when each thrombus has a certain probability of embolizing, the overall likelihood would increase with the number of veins

involved. From this finding it does not logically follow that DVT patients with Factor V Leiden have a decreased incidence of PE. Moreover, the number of affected veins was not different in patients with isolated DVT or both DVT and PE.

It should be noted that it is impossible to study the effect of the location and thrombus size in patients with isolated PE and that individuals with both DVT and PE have been used as a surrogate for the isolated PE population.

Growth speed

Factor V Leiden mice had faster growing thrombi compared with non-Factor V Leiden mice [26]. We studied growth speed in two ways, both epidemiologically and *in vitro*. First, we studied whether time between a clear thrombus provocation such as surgery, injury or travel, and diagnosis was similar in carriers versus non-carriers and found no difference. It took slightly more time to diagnose PE than to diagnose DVT. As a consequence it will be unlikely that the presence of Factor V Leiden will have resulted in earlier treatment and a reduction in risk of embolization. Secondly, we studied the growth speed by measuring clotting time *in vitro*. No differences were found between Factor V Leiden carriers and non-carriers in clotting time, nor was there a difference between PE and DVT patients. However, care should be taken in interpreting these results as the in vitro clotting was performed without the presence of activated protein C. Thus the effect of Factor V Leiden may not have become apparent by using this assay. Due to this limitation we cannot exclude a possible difference in growth speed of the thrombus as an explanation for the Factor V Leiden paradox. As mouse models have shown an increased speed of thrombus formation in Factor V Leiden mice and patients with PE had a longer time interval between provocation and diagnosis, there might be a relation. It should therefore be investigated more extensively whether the duration of thrombus formation could explain the Factor V Leiden paradox.

Thrombus density

Finally, we studied whether a difference in thrombus density could shed light on the Factor V Leiden paradox. We found that Factor V Leiden carriers had a slightly lower thrombus density than non-carriers. The results combined with the higher number of affected veins might suggest a different composition of the thrombus. Yet, no differences in thrombus density were found between patients with DVT or PE. Therefore, thrombus density does not seem to offer an explanation for the Factor V Leiden paradox.

Conclusion

These results confirm the existence of the Factor V Leiden paradox. However, none of the above mechanisms seems to be a solid explanation of the Factor V Leiden paradox. Future research might focus on a possible difference in growth speed and composition of the thrombus as these represent the most promising explanation.

Acknowledgement

We thank the directors of the Anticoagulation Clinics of Amersfoort (M.H.H. Kramer, MD), Amsterdam (M. Remkes, MD), Leiden (F.J.M. van der Meer, MD), The Hague (E. van Meegen, MD), Rotterdam (A.A.H. Kasbergen, MD), and Utrecht (J. de Vries-Goldschmeding, MD) who made the recruitment of patients possible. The interviewers (J.C.M. van den Berg, B. Berbee, S. van der Leden, M. Roosen, and E.C. Willems of Brilman) performed the blood draws. We also thank I. de Jonge, MSc, R. Roelofsen, MSc, M. Streevelaar, L.M.J. Timmers, MSc, and J.J. Schreijer for their secretarial and administrative support and data management. The fellows J.W. Blom, MD, A. van Hylckama Vlieg, PhD and L.W. Tick, MD, took part in every step of the data collection. C.J.M. van Dijk, R. van Eck, J. van der Meijden, S. Moschatsis, P.J. Noordijk and T. Visser performed the laboratory measurements. H.L. Vos supervised the technical aspects of DNA analysis. Finally we would like to thank J.P. Vandenbroucke for his advises regarding the analyses. We express our gratitude to all individuals who participated in the MEGA study. This research was supported by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992) and the Netherlands Organisation for Scientific Research (912-03-033| 2003). The funding organizations did not play a role in the design

and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript. None of the authors has a potential conflict of interest.

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Chapter 8

Discussion & Summary

Venous thrombosis is a common disease affecting millions of individuals each year. The aim of this thesis was to investigate risk factors for venous thrombosis related to stasis of the blood. Stasis has already been described in general terms as a risk factor in 1856. So far only a few studies have been conducted to show whether the opposite of stasis, exercise and early ambulation after bed rest, decrease the risk of venous thrombosis.

The history of ambulation and venous thrombosis risk

The number of days that women were advised to stay in bed after child birth has rapidly declined between 1880 and 1980. We wondered whether this change was due to research showing that long periods of bed rest were responsible for the high rates of venous thrombosis at the beginning of the twentieth century. Surprisingly, in **chapter 2** we showed that not the high risk of venous thrombosis but practical reasons were responsible for the large reduction in number of days women were bedridden. During and after the Second World War the babyboom resulted in a shortage of hospital beds. To ensure that all women could have their child delivered in the hospital, women had to leave the hospital shortly after giving birth. This was unusual before the war. Some safety studies showed that more venous thrombosis events occurred in the bedridden group compared with the ambulated group. However, only healthy women were allowed to leave the bed, while the ones with complications had to remain bedridden. Furthermore, other factors such as anticoagulation use and the age of child-bearing women, changed during the same period. For these reasons it remains unknown whether early ambulation is responsible for the decrease in the number of venous thrombotic events or whether this decrease was the result of other factors.

Although it is generally believed that venous thrombosis rates have dropped due to earlier ambulation of postpartum women, we were surprised that we could not find an evidence-based study showing that ambulation was the main reason. We do not suggest that more research is needed to study whether extended bed rest would be more beneficial compared with early ambulation. However, we do believe that it is important to note that other factors than evidence based studies have played a major role in the past in shaping the currently used practice.

Study designs

Chapters 2 to 7 focus on exercise and immobilization and the risk of venous thrombosis. We have described the results of two large observational studies; the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study (MEGA study) in **chapters 3, 4, 6** and **7** and the Cardiovascular Health Study (CHS) in **chapter 5**.

The CHS is a large cohort study of risk factors for cardiovascular disease among elderly individuals. In 1989, 5201 individuals over 65 years of age were included in this study. In 1992, 687 African-Americans of the same age joined the study population. Information on exercise, general health and other risk factors for cardiovascular disease was obtained via questionnaires and interviews while weight and height were measured during visits to the clinics in 1989, 1992 and 1997. Up to 2001, at total of 171 first life-times venous thrombotic events were recorded.

The MEGA study is the largest population-based case-control study among individuals with a first venous thrombosis. A total of 5050 eligible patients and 6000 control subjects participated all aged between 18 and 70 years. Exercise, surgery, minor injuries, weight and height were assessed in a standardized self reported questionnaire. As malignancy is a major risk factor for venous thrombosis and affects behaviour to a large extent, participants with malignancy were excluded from the analyses presented in this thesis.

Control groups

A strength of the MEGA study is the inclusion of two different control groups. Partners of the patients were asked to serve as a control group and a random digit dialling control group was also included. The latter group was frequency matched on age and sex of the patients, while the partner control group was “matched by nature” on age and (the opposite) sex. Few studies have included multiple control groups. Both control groups have their own advantages and disadvantages. Some of the major differences will be discussed.

Partner controls have the advantage of a high participation rate. Partners are eager to participate as they have seen the consequences of the disease with their partner. In the MEGA study, this is reflected by the high participation rate (80%) compared with the participation rate in the random control subjects (69%). Our partner control group will therefore be a good reflection of the overall partner population. Patients and their partners will often jointly fill in the questionnaire. As the patient has the "serious event" partners may less often "complain" on more minor events. This might be a reason that partners reported less often minor injuries compared with random control subjects (**chapter 5**). A third difference between the partner and random control subjects is that obviously the partner controls have a partner while not every random control subject has a partner. Couples often have a higher social economic status and being in a relationship might affect life style resulting in, for instance, a more frequent use of oral contraceptives and being pregnant. Finally, besides that being in a relationship affects lifestyle, couples usually have similar habits as they have a similar background. This could result in similar habits regarding sports activities, food, alcohol and smoking use, educational level and social economic background. We showed in **chapter 4** that patients and partners indeed have similar exercise habits. For this reason, it is important to perform matched analysis when analysing couples. Even unmeasured confounders will be taken into account. Consequently the estimate will then be very specific in estimating the effect of the exposure variable itself. However, performing a matched analysis has multiple drawbacks. The analysis may lead to a risk estimate that will be too close to one due to overmatching, as this analysis also adjusts for possible intermediate variables such as food and smoking habits. A second drawback is a large reduction in power, as only couples can be included with complete information on all factors that are included in the analysis. Single patients or partners of excluded patients can also not be included in this analysis, leading to a loss of power.

Random control subjects were recruited in the same geographical area as the patients and were frequency matched on age and sex. We specifically asked for an individual with a specific age and sex characteristic to avoid a response from very healthy or sick individuals only. Individuals who are able to pick up the telephone the quickest in a household may be

healthier than the average person in that particular household, or, alternatively, might be those who are home because of an illness. Although we avoided this bias, in general, individuals who participate in medical research are more likely to be highly educated, young, female and have a high social economic status compared with the general population[1]. Furthermore it is possible that the participating controls are very interested in health related issues. This will probably have occurred more often in the random control subjects compared with the partner control subjects. Compared with partner controls, random controls more often had had surgery and were relatively more often pregnant (personal communication).

In our study both control groups were included. For calculation of the overall risk a pooled odds ratio was calculated in which the odd ratio of the matched analysis in the couples was combined with the odd ratios of the random control individuals with all patients. This included an adjustment for the patients who were included in both analyses. By calculating a combined estimate we believe that we have evened out the disadvantages of both control groups and obtained an optimal estimate.

Exercise and the risk of venous thrombosis

In the MEGA study we showed that participation in exercise on a regular basis decreased the risk of venous thrombosis (Odds ratio [OR] adjusted for age, sex and body mass index 0.71 95% confidence interval [CI] 0.64-0.78). Relative risks were similar in men and women and in young (<40 years), middle aged (40-60 years) and older (60-70 years) individuals. No differences in risk reductions were found for strenuous compared with moderate intense activities or for different frequencies of exercise. Sports activities with a high injury risk were less beneficial than sports activities with a low injury risk (**chapter 3**). This beneficial effect of participating in exercise was also shown in a case-control study among young women[2]. In contrast, in CHS participating in exercise increased the risk of venous thrombosis (OR adjusted for age, sex and body mass index 1.38, 95%CI 0.99-1.99). A dose response relationship was found which showed that strenuous intensity exercise or spending large amounts of kilocalories on exercise increased the risk of venous thrombosis

compared with mild intensity exercise and spending fewer amounts of kilocalories on exercise (**chapter 4**). Another cohort study with a follow up of 20 years among physicians over 45 years of age also found a slightly increased risk of venous thrombosis with increasing amounts of exercise [3].

These results suggest a discrepancy between the case-control studies and cohort studies on the risk of venous thrombosis associated with exercise. Multiple reasons for this difference are possible. Firstly, both cohort studies have been performed in older individuals compared with the two case-control studies. Various other studies have shown that risk factors in the young and middle-aged do not necessarily cause a similar risk in older individuals. For venous thrombosis both coagulation[4] and environmental risk factors[5] have shown different effects in the young versus the old. In arterial disease it has frequently been shown that risk factors that cause a disease at a younger age can be preventive in the very old. This is called "reverse epidemiology" and has been found for high levels of cholesterol[6;7] and high blood pressure[8;9]. Reverse epidemiology may also be present in the case of exercise and the risk of venous thrombosis. However, the odds ratios in the different age groups in the MEGA study do not suggest a difference in risk for those between the age of 60 to 70 and those less than 50 years of age. For this reason "reverse epidemiology" seems less likely, although it may still be present at even older ages.

A second reason for the opposite results in the association of exercise and venous thrombosis risk might be the study design. Case-control studies assess exercise after the event while cohort studies assess participation in exercise prior to the event. Both methods have drawbacks. A disadvantage of case-control studies is that patients have knowledge of the event. If cases would be more "honest" on their exercise compared with control subjects, control subjects might report the intensity of exercise they wish to perform, rather than the actual exercise, thus over reporting exercise, resulting in recall bias. Furthermore, it is possible that patients report their exercise after the venous thrombosis instead of the amount of exercise prior to the event. In a cohort study, however, exercise is assessed prior to the venous thrombosis, and particularly in those with extended follow-up, the reported

intensity of exercise might not be representative of the circumstances just prior to the venous thrombosis. In that situation, case-control studies would be better since they assess sports habits closer to the event.

The contradictory results obtained in epidemiologic studies are not solved by knowledge of the possible mechanism of exercise obtained in laboratory studies. The beneficial coagulant state in individuals who exercise regularly[10;11] suggests a positive effect of exercise. However, as venous thrombosis is an acute disease, the increased procoagulant state during and shortly after exercise[12] might be the last drop leading to the formation of a clot.

Several studies have shown that exercise is beneficial for longevity in general[13;14] and is associated with a lower risk of arterial cardiovascular diseases[15] which will probably outweigh an increased risk of venous thrombosis. However, we do believe that an explanation for the discrepancy in the results is needed. Studies that would include for example old individuals in case-control studies or young individuals in cohort studies might improve knowledge on both the mechanism of exercise as well as the prevention of venous thrombosis.

Paget-Schrötter syndrome

In **chapter 5** we studied whether participating in exercise that mainly involve the arms increased the risk of venous thrombosis of the upper extremities as various case reports have suggested[16;17]. We found that participating in arm-sports increased the risk of arm thrombosis compared with participating in other sports (OR adjusted for age, sex and body mass index 1.79, 95% CI 0.75-4.29). The risk of performing arm-sports was similar with performing no sports at all (OR adjusted for age, sex and body mass index 1.08 95% CI 0.63-1.87). The most striking aspect of the study was the difference in thrombus location. In patients who did not exercise or did not participate in arm-sports, most venous thrombi occurred in the left arm (64% left arm). However, among those who participated in arm-sports, most thrombi occurred in the right arm (33% left arm). Therefore participating in arm-sports only increased the risk of venous thrombosis in the right arm (OR 2.0 95%CI

0.97-4.33) but not in the left arm. As the right arm will be the dominant arm in most cases, this suggests that overdevelopment of the muscles in the dominant arm due to for example playing tennis can lead to thrombus formation in that arm. However, the risk of venous thrombosis was decreased in the left arm due to the general benefits of exercise. Venous thrombosis of the arm is a very rare disease and therefore these results should not lead to public health advice.

Minor injuries and the risk of venous thrombosis

In **chapter 6** we showed that minor injuries of the leg such as ankle and knee sprains increased the risk of venous thrombosis five-fold (OR 5.1, 95%CI 3.9-6.7). As minor injuries occurred in approximately 4 percent of the control subjects, they are relatively common. Therefore, they are responsible for about 8 percent of all venous thrombotic events and are major contributors to the risk of venous thrombosis. A local effect of minor injuries was found; injuries in the leg increased the risk of venous thrombosis five-fold, while injuries located in other body parts did not increase the risk. This local effect suggests that alterations of the coagulation system by injuries are not responsible for the increased risk. One study showed that although injuries affect the coagulation system, the levels of coagulation factors in trauma patients were not predictive of the actual occurrence of venous thrombosis[18]. If the coagulation system is not responsible, this suggests that stasis is probably the primary cause of venous thrombosis. Stasis might occur by reduced mobility due to pain or compression of the vein due to oedema, however, other factors may play an additional role. Although there is a continuous debate whether venous thrombosis is also affected by damage of the vessel wall[21], the high local risk caused by injuries suggests that vessel wall damage might play a role in the thrombus formation after injury.

Injuries increased the risk of venous thrombosis especially in individuals who had a genetic predisposition or a family history of venous thrombosis. A 40- to 50- fold increased risk in these patients was found. The risk of venous thrombosis was highest in the first month after the injury and decreased sharply thereafter. For this reason we believe that many cases of venous thrombosis could be prevented when high risk individuals with injuries would receive prophylactic treatment. The number of patients with an injury and a genetic

predisposition of venous thrombosis that would require short term prophylactic treatment to prevent one case of venous thrombosis would be only 25. Although we believe that this rate may outweigh the increased risk of bleeding during this short period, data are scarce and future research is needed to show whether short term prophylactic treatment in individuals with injuries is safe.

The Factor V Leiden paradox

As shown in **chapter 6**, injuries had a local effect. Injuries were found to be a strong risk factor for deep venous thrombosis of the leg, while only a modest risk factor for pulmonary embolism. This brings us to the discussion whether deep venous thrombosis and pulmonary embolism can be considered a single disease. In an attempt to shed more light on this issue, Factor V Leiden and the risk of pulmonary embolism versus deep vein thrombosis of the leg was studied. Carriers of the factor V Leiden mutation had a highly increased risk of deep venous thrombosis of the leg while the risk of pulmonary embolism was only mildly increased. This phenomenon has been called the Factor V Leiden paradox. Although this paradox has been known for some time no explanations have been identified. In **chapter 7** several mechanisms for the factor V Leiden paradox were investigated. We used five different approaches; location of the thrombus in the leg, number of affected veins, time until diagnosis of the thrombosis, *in vitro* coagulation time and clot density; and could be ruled out as possible explanations for this paradox. This suggests that other factors must play a role. Future research should focus on the formation of the clot *in vivo* which might provide a better insight into the characteristics of the different types of clot and might give information on the adherence to the vessel wall.

So far only a few studies have investigated whether other risk factors, besides Factor V Leiden, lead to a different risk of pulmonary embolism compared with deep vein thrombosis of the leg. In two case-control studies [22;23] and a follow-up study [24], surgery resulted in more cases of pulmonary embolism compared with deep vein thrombosis of the leg.

We believe that providing more information on the risk factors for venous thrombosis of the leg and pulmonary embolism separately is important. Pulmonary embolism is considered a dangerous result of venous thrombosis as it can lead to death. If a risk factor more often results in pulmonary embolism than in deep vein thrombosis prophylactic therapy could be prescribed more frequently to individuals with that specific risk factor. Furthermore, the estimate of a relative risk is often based on a combination of the risk estimates for pulmonary embolism and deep venous thrombosis. If in a certain population the ratio of pulmonary embolism and deep venous thrombosis of the leg is different, the estimate of the relative risk will be different. Therefore, both physicians and researchers should consider this aspect when identifying risk factors for venous thrombosis.

Conclusions

The aim of this thesis was to investigate exercise and immobilization as factors affecting the risk of venous thrombosis. In the various chapters we showed that although stasis is an important risk factor, this does not automatically imply that the inverse, exercise, prevents venous thrombosis. We believe that we have given more insight into several aspects on the etiology of venous thrombosis and hope that we have encouraged researchers to solve the questions raised in this thesis.

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Samenvatting

Veneuze trombose is een veel voorkomende ziekte. Jaarlijks krijgt ongeveer 1 op de 1000 mensen een trombosebeen of een longembolie wat neerkomt op ongeveer 16 duizend gevallen ieder jaar in Nederland. Bij een trombosebeen ontstaat er een bloedstolsel in de aderen van het been. Soms breekt (een deel van) het stolsel af welke via het hart in de longen terecht komt. De slagaderen van de longen worden hierdoor, afhankelijk van de grootte van het stolsel, geheel of gedeeltelijk afgesloten van bloed. Een longembolie is daarom ook gevaarlijk, in 1 a 2 procent van de gevallen leidt het tot de dood.

Er zijn verschillende oorzaken van veneuze trombose en ze zijn reeds in 1856 door de Duitse arts Virchow opgedeeld in drie categorieën; veranderingen in de samenstelling van het bloed, schade aan de vaatwand, en stilstand of stase van het bloed. Dit proefschrift gaat voornamelijk over de relatie tussen stase en veneuze trombose. Hiervan is al heel lang bekend dat het kan leiden tot veneuze trombose. Zo hebben vele studies al laten zien dat geïmmobiliseerd zijn in schuilkelders, vliegtuigen en ziekenhuisbedden het risico op veneuze trombose verhoogd.

Rond het jaar 1900 lagen kraamvrouwen ongeveer een maand op bed na de bevalling. Dit gebeurde om een aantal redenen maar de voornaamste reden was een grote angst voor verzakkingen (prolapses); het naar beneden zakken van de organen wanneer de vrouw te vroeg op zou staan. Door de jaren heen is het aantal dagen dat een vrouw na de bevalling op bed moet doorbrengen sterk gedaald. Wij hebben in **hoofdstuk 2** onderzoek gedaan naar de redenen voor deze afname en of zij iets te maken had met een mogelijke verlaging van het voorkomen van veneuze trombose. Veneuze trombose is namelijk een belangrijke complicatie tijdens en kort na de zwangerschap. Rond het jaar 1900 kregen ongeveer 8 op de 1000 vrouwen in het kraambed een longembolie, terwijl dit tegenwoordig vele malen lager ligt. Wij hadden dan ook de verwachting dat deze hoge prevalentie in 1900 invloed zou hebben op het beleid omtrent de tijd die vrouwen in bed moesten doorbrengen omdat Virchow immers had laten zien dat veneuze trombose werd veroorzaakt door immobilisatie. Aanvankelijk leek het daar ook op. Aan het begin van de 20ste eeuw waren er verscheidene Duitse artsen die opperden dat het vroeg mobiliseren na een kraambed gunstig zou zijn voor het risico van veneuze trombose en pasten dit in hun eigen kliniek toe. Dit vond echter

geen weerklank in de rest van de wereld waardoor deze praktijk weer verdween tot aan de tweede wereld oorlog. Tijdens de oorlog in de Verenigde Staten en kort na de oorlog in (West) Europa kwam de zogenaamde "babyboom" welke zorgde voor een groot tekort aan ziekenhuisbedden. Om toch alle vrouwen de kans te geven om in het ziekenhuis te bevallen werden vrouwen steeds sneller na de bevalling naar huis gestuurd. Omdat de angst voor prolapsen ongegrond bleek werd deze praktijk na de oorlog behouden. De praktijk in Nederland was daarnaast nog iets anders doordat de vrouwen na de oorlog steeds vaker thuis gingen bevallen. Vrouwen die thuis hun kind kregen zullen naar alle waarschijnlijk vaker zelf het bed verlaten hebben waardoor het beleid iets minder strikt geweest zal zijn dan in de ziekenhuizen. Wat ons opviel, was dat er geen goed onderzoek is verricht naar de effecten van het vroege opstaan op het risico van veneuze trombose. Vaak werden de ziekere vrouwen die op bed moesten blijven liggen vergeleken met de gezondere vrouwen die uit bed mochten. Daarnaast waren er nog belangrijke andere veranderingen zoals de jongere leeftijd waarop vrouwen kinderen kregen en het gebruik van antistollingsmedicatie welke beiden het risico op veneuze trombose verlaagden. Hierdoor weten we nog steeds niet of het vroeger opstaan uit het kraambed en eerder in beweging komen verantwoordelijk waren voor de verlaging van het aantal gevallen van trombose na de bevalling.

Behalve rustig bewegen na een bevalling zouden ook bewegen en sporten het risico op veneuze trombose bij algemene bevolking kunnen verlagen. Wij hebben dit op twee manieren onderzocht; in een groot patiënt-controle onderzoek en in een groot cohort onderzoek. In **hoofdstuk 3** hebben we gekeken binnen de MEGA studie, een groot Nederlands patiënt-controle onderzoek waarin alle opeenvolgende patiënten tussen de 18 en de 70 jaar met een eerste veneuze trombose tussen 1999 en 2004 uit 6 verschillende trombosediensten in de Randstad werden geincludeerd. We hadden tevens twee verschillende controle groepen verzameld; partners van patiënten werden gevraagd om deel te nemen alsmede een random controle groep uit de algemene populatie. In de MEGA studie hebben we laten zien dat het regelmatig deelnemen aan sporten het risico op veneuze trombose verlaagd. Deze verlaging van het risico was hetzelfde voor verschillende types, soorten en frequenties van deelname aan sport, voor mannen en vrouwen en in verschillende leeftijdsgroepen. In **hoofdstuk 4** maakten we gebruik van de Cardiovascular

Health Study. Dit is een groot Amerikaans cohort uit 1989 waarin 5201 65-plussers werden geincludeerd, welke werden gecomplementeerd met 687 oudere Afro-amerikanen in 1993. Van deze ouderen werden op verschillende momenten vragenlijsten met betrekking tot sport gewoontes afgenomen. Daarnaast werden alle veneuze tromboses geregistreerd tot en met 2001. In deze studie vonden we dat sporten het risico op veneuze trombose verhoogde. De verschillende resultaten tussen beide studies kunnen meerdere oorzaken hebben. In de eerste plaats is er natuurlijk het leeftijdsverschil. Verschillende andere risicofactoren voor arteriële trombose zoals hoge bloeddruk en roken hebben al laten zien dat iets een risicofactor kan zijn in een jongere populatie terwijl binnen de oudere populatie deze factor juist lijkt te beschermen. Dit verschijnsel wordt ook wel “reverse-epidemiology” genoemd. Dit zou ook het geval kunnen zijn voor sporten en veneuze trombose; het zou beschermend kunnen werken in de jongeren terwijl het juist gevaarlijk is bij ouderen. Sporten heeft namelijk een tweeledig effect, aan de ene kant heeft het een gunstig effect op de bloedstolling en aan de andere kant is er een grotere kans op blessures. In de MEGA studie vonden we een minder gunstig effect van blessure gevoelige sporten op het risico van trombose vergeleken met blessure ongevoelige sporten. Bij ouderen zouden de negatieve effecten op blessures niet kunnen opwegen tegen de positieve effecten op de bloedstolling terwijl dit bij jongeren nog wel het geval zou kunnen zijn.

Naast blessures zouden er ook nog andere negatieve effecten van sporten kunnen zijn. Verschillende patiëntbeschrijvingen hebben gesuggereerd dat intensief gebruik van de armen door bewegen zou kunnen leiden tot het zeer zeldzame armtrombose (Paget-Schrötter syndroom). De grote armvene moet namelijk de nauwe uitgang uit de borstkas delen met een spier en een slagader. Wanneer deze spier nu te groot wordt door intensief gebruik zou dit kunnen leiden tot verdrukking van de ader welke vervolgens zou resulteren in veneuze trombose. Er was echter nog nooit goed onderzoek gedaan of arm-sporten ook daadwerkelijk het risico op armtrombose verhoogde. Wij hebben dit dan ook onderzocht in **hoofdstuk 5**. Binnen een relatief grote groep van patiënten met een trombosearm hebben we gekeken of sporten die voornamelijk met de benen worden gedaan en sporten waarbij vooral de armen werden gebruikt het risico op trombose veranderden ten opzichte van het niet sporten. Wij vonden dat been-sporten het risico op veneuze trombose verlaagden ten

opzichte van het niet-sporten, terwijl arm-sporten geen invloed hadden op het risico. Wel bleek er een verschil te zijn in de locatie van de trombose; in niet-sporters was de trombose voornamelijk in de linkerarm terwijl bij armsporters de trombose voornamelijk in de rechterarm was. Dit suggereert dat er toch sprake kan zijn van een bepaalde mate van overontwikkeling van de armspieren omdat de rechterarm waarschijnlijk voor de meeste mensen de dominante arm is. De kans op een trombosearm blijft echter erg klein. Daarnaast was het risico op een trombosearm niet hoger in mensen die een armsport deden dan in mensen die helemaal niet sporten. Het is daarom niet nodig om mensen te adviseren geen armsporten meer te doen.

Van zwaar trauma is al heel lang bekend dat ze het risico op veneuze trombose sterk verhoogd. Van alle mensen die bijvoorbeeld overleden na een auto-ongeluk stierf uiteindelijk ongeveer 30 procent aan een longembolie. Daarnaast is bekend dat een gebroken bot, achillespeesruptuur en vergelijkbare vormen van blessures het risico op trombose sterk verhogen. Echter, behalve de blessure zelf, spelen bij dergelijke zware blessures ook nog andere mogelijke oorzaken van veneuze trombose een rol zoals operaties, langdurige immobilisatie door bedrust en gips. Van het risico van kleine kwetsuren waarbij deze andere factoren geen rol spelen was echter tot op heden nog weinig bekend. Wij hebben dit dan ook onderzocht in **hoofdstuk 6**. Wij vonden binnen de MEGA studie dat kwetsuren het risico op veneuze trombose drievoudig verhoogden. Dit effect bleek erg lokaal; blessures in het been verhoogden het risico vijfmaal, terwijl blessures op andere locaties zoals de armen geen enkele invloed hadden op het risico. Ook bleek het effect van blessures zeer tijdelijk, het risico was sterk verhoogd in de eerste 4 weken na de blessure, terwijl het extra risico verdwenen was na 10 weken. Wanneer mensen naast de blessure ook nog een erfelijke risicofactor hadden voor veneuze trombose, bijvoorbeeld de Factor V Leiden mutatie, bleek het risico sterk verhoogd; ten opzichte van mensen zonder blessure en zonder deze mutatie hadden deze mensen een 40 tot 50 keer verhoogd risico. Meer onderzoek is daarom wenselijk om te bepalen of deze groep mensen beschermd zou kunnen worden tegen het optreden van een trombose door bijvoorbeeld profylaxe en of deze bescherming opweegt tegen het verhoogde bloedingsrisico.

In het laatste hoofdstuk, **hoofdstuk 7**, hebben we gekeken naar de Factor V Leiden paradox. Van deze erfelijke risicofactor voor veneuze trombose is bekend dat hij het risico op het krijgen van een trombosebeen sterk verhoogd. Uit steeds meer onderzoek blijkt echter dat deze erfelijke factor het risico op een longembolie in veel mindere mate verhoogd. Dit is opvallend omdat we trombosebenen en longembolieen immers beschouwen als twee uitingen van dezelfde ziekte. In hoofdstuk 7 hebben we dan ook gezocht naar een mogelijke verklaring voor deze paradox. Leidt het hebben van de factor V Leiden mutatie bijvoorbeeld tot een andere locatie van de trombose welke op zijn beurt minder gevoelig is om te emboliseren. Wij hebben 5 verschillende mogelijke mechanismen onderzocht; de locatie en grootte van de trombus, de tijd tussen provocatie van de trombose en de daadwerkelijke diagnose (de groeisnelheid), en twee labbepalingen; de stollingstijd en de dichtheid van het stolsel. Geen van deze mogelijke mechanismen gaf echter een sluitende verklaring, hoewel de groeisnelheid van de trombus de meest veelbelovende factor is om in de toekomst verder onderzoek naar te doen.

Tot slot; bij het begin van ons onderzoek naar veneuze trombose en beweging leek het eenvoudig; als stase het risico op veneuze trombose verhoogd, dan zal beweging het risico op veneuze trombose wel verlagen. In dit proefschrift hebben we laten zien dat het niet zo eenvoudig ligt en dat er wellicht meer vragen opgeroepen zijn dan beantwoord. Toch hopen we dat we met dit proefschrift een bijdrage hebben kunnen leveren aan de kennis over het ontstaan van veneuze trombose en dat we andere onderzoekers hebben kunnen enthousiasmeren om de vragen die dit proefschrift wellicht oproept te beantwoorden.

Dankwoord

Promoveren is een geweldige kans en mogelijkheid. Hoewel er soms wordt gezegd dat je het alleen doet, leert de praktijk wel anders. Ik wil iedereen die me heeft geholpen dan ook bedanken.

Een paar mensen wil ik speciaal noemen. Als eerste mijn familie. Jullie hebben de basis gelegd voor wie ik ben. Carla, jij hebt me leren praten, lezen, schrijven en rekenen. Hans, jij hebt me de liefde voor de getallen en het beredeneren gegeven dus dit had ik niet zonder jullie kunnen doen. Maartje en Haike, jullie zijn geweldige zussen!

Verder, vrienden en vooral vriendinnen, allemaal ontzettend bedankt! De 'squash dames' – Marinka, Sandra, Saskia en Willeke– nog maar twee promoties te gaan dus misschien scheelt dat in de agressie, dank voor de etentjes en gezelligheid niet alleen op de baan maar vooral daarbuiten. Amber, Eef en Jacque, bedankt voor alle telefoontjes en vooral voicemails.

Op dit boekje sta ik dan wel alleen, bij de MEGA-studie is dat zeker niet het geval. Ingeborg, Liesbeth, Lucie, Petra, Rob en jullie voorgangers, zonder jullie was de MEGA nooit zo'n succes geworden. "Mijn" stagiaires – Liz, Angela en Arwin – ik heb ontzettend veel van jullie geleerd, hopelijk jullie ook van mij. Alle (staf)leden van de klinische epidemiologie; ik vond de kennismaking met de epidemiologie een openbaring. Bedankt dat jullie me deze geweldige "Leidse" basis hebben gegeven. Ik hoop er nog vele jaren van te kunnen genieten. Susan Heckbert and to all those from the CHRU, thank you all for the wonderful experience I had in Seattle, love to see you all again. Ook wil ik iedereen van binnen en buiten de afdeling klinische epidemiologie (vooral Alette, Irene, Saskia, Yael en Yvonne S) bedanken voor alle gezelligheid, praatjes, koffiepauzes, lunches en borrels. En bovenal mijn kamergenoten van C9-20; Carla en Stella en van C9-36, Yvonne, Martijn, Nora, JJ, en Mirjam, het enige wat ik kan zeggen is *C9-36 enhancing your PhD experience*.

Mijn paranimfen. Elisabeth, samen begonnen, heel veel telefoontjes, (ontslag)brieven, vragenlijsten, cleanen, koppelen, frustraties en gelachen en tot slot (bijna) samen geëindigd. Super dat je ook een beetje ‘samen’ wilt verdedigen. Sanne, bedankt voor je wijntjes, films, Johan-cd’s, kaartjes, en dat je er, zoals altijd, ook nu weer bent als paranimf.

Lieve lieve Joris, zonder jouw liefde, geduld, aandacht en relativeringsvermogen had ik dit nooit gehaald. Dankjewel dat je bent zoals je bent, en vooral dat je bij mij wilt zijn!

Curriculum Vitae

Karlijn van Stralen werd op 17 januari 1980 geboren te Delft. Van 1985 tot 1987 verbleef zij met haar familie in Guinee Bissau. Na het behalen van haar VWO diploma aan de scholengemeenschap De Amersfoortse Berg te Amersfoort in 1997 ging zij Voeding en Gezondheid studeren aan de Landbouwuniversiteit te Wageningen. In het bezit van haar propedeuse diploma besloot zij in 1998 over te stappen op de studie Medische Biologie aan de Vrije Universiteit te Amsterdam. Tijdens deze studie heeft zij diverse stages gelopen, onder andere bij Numico Research te Wageningen en bij het IOC dopinglaboratorium te Lissabon, Portugal.

Na haar afstuderen in augustus 2003 begon zij op 1 september van hetzelfde jaar aan haar promotie onderzoek onder leiding van Prof. Dr Frits Rosendaal en Dr Carine Doggen op de afdeling Klinische Epidemiologie van het Leids Universitair Medisch Centrum. Daar heeft zij zich gericht op dataverzameling en analyses in de Multiple Environmental en Genetic Assessment of risk factors for venous thrombosis (MEGA study). Tijdens haar promotie onderzoek heeft zij in het kader van de Leducq International Network Against Thrombosis drie maanden gewerkt aan de Cardiovascular Health and Research Unit (University of Washington, Seattle, USA), welke onder leiding staat van Prof. Dr Bruce Psaty en Prof. Dr David Siscovick. Daar heeft zij onder begeleiding van Prof. Dr Susan Heckbert onderzoek verricht aan the Cardiovascular Health Study. De resultaten van beide studies staan beschreven in dit proefschrift.
Zij volgde verscheidene epidemiologische cursussen waaronder de Boerhaave cursus “Klinische Epidemiologie” op Schiermonnikoog (feb 2004), de NIHES cursus “Analysis of time-varying exposures” in Rotterdam (feb 2006), en de cursus “Survival Analysis” van Prof David Hosmer in Rome (dec 2007).

Sinds september 2007 werkt zij als post-doc bij de afdeling Klinische Informatiekunde aan het Academisch Medisch Centrum te Amsterdam. Onder leiding van Dr Kitty Jager verricht zij onderzoek aan de ERA-EDTA registratie voor dialyse en transplantatie patiënten in Europa. Daarnaast is zij bezig een vergelijkbare registratie op te zetten voor kinderen op dialyse en transplantatie in Europa.