Physical activity, immobilization and the risk of venous thrombosis

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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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