Air travel and venous thrombosis. Results of the WRIGHT study. Part II: Mechanism

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Summary and Discussion

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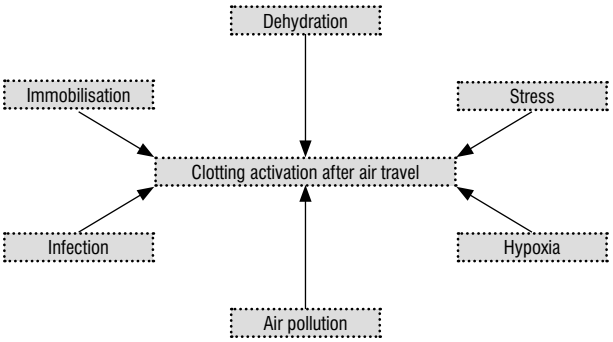
Air travel has become a well-known risk factor for venous thrombosis with a two- to four fold increased risk, an absolute risk of 1 in 4600 long-haul flights and a dose-response relationship with both duration as well as number of flights (1-10). Ever since the awareness of thrombosis after air travel intensified, the interest in its risk factors increased accordingly. Potential risk factors for venous thrombosis after air travel can be separated into passenger characteristics or aspects of the environment in the cabin of the aircraft. Environmental factors in the cabin are the cramped position that passengers are exposed to, in particular passengers who are short, tall or obese, as well as hypobaric hypoxia and possibly also mild dehydration (11-14). Passenger characteristics are the above mentioned anthropomorphic factors, behavioural factors, sex, oral contraceptive use, and coagulation defects, such as the factor V Leiden mutation and high levels of prothrombin (factor II) and clotting factors VIII and IX (1;7;15)(**chapter 2**).

In this thesis we studied the pathophysiology that underlies the risk as well as the effect of behaviour of passengers on the risk of thrombosis after air travel. To study the pathophysiology, we conducted a case-crossover study in which we investigated the effect on the coagulation system of 8 hours of air travel, 8 hours of immobilisation in a cinema and 8 hours of daily activities in 71 volunteers (**chapter 3-6**). Behaviour of passengers was studied in the MEGA study, a large population based case-control study on risk factors of venous thrombosis. The study included 11033 participants who received a questionnaire on risk factors for venous thrombosis, including recent travel history and details of their last flight. From this population, eighty patients and 108 controls were selected who had recently (<8 weeks) travelled for more than 4 hours by airplane (**chapter 7**).

One of the main outcomes of the case-crossover study was the increase in markers of clotting activation in 17% of the subjects after the flight exposure (particularly in thrombin-antithrombin complexes (TAT)), compared to 3% of the subjects after the cinema exposure and 1% after the daily life situation. This was most evident in women who used oral contraceptives and who were also carriers of the factor V Leiden mutation (**chapter 3**). We explored several hypotheses that could explain the high response in TAT in these subjects. Figure 1 gives an overview of possible mechanisms. The center box represents the coagulation activation that we found in 17% of our volunteers. This is the central point from which we hypothesized on the mechanisms that possibly underlie coagulation activation after air travel. The several hypotheses are further discussed below.

Figure 1. Possible explanations for coagulation activation during air travel.



Immobilisation. The most obvious explanation for air-travel-related thrombosis is immobilisation. Passengers are restricted to limited space, resulting in a prolonged cramped position during long-haul flights. Reports of venous thrombosis after long term sitting are known since World War II when a high incidence of pulmonary embolism was reported in individuals who sought shelter in the underground during the bombing of London (16). More recently, several cases of venous thrombosis were reported after extreme traffic jams during a strike of French public transport (17). Also, a high rate of pulmonary embolism was found after an earthquake in Japan when people hid in their cars for days (18). The term eThrombosis was introduced to describe the occurrence of venous thrombosis after extended use of the computer (19). Our review showed that pathophysiologic studies into the effect of prolonged immobilisation found either no effect or a decrease in markers of thrombin generation (e.g. prothrombin fragment 1 + 2 (F1+2) or thrombin anti-thrombin complex (TAT), **chapter 2**). The risk of venous thrombosis after air travel was found to be increased in those who are tall, short or overweight (1;10), which strongly suggests a causal role for immobilisation. Furthermore, in **chapter 7** we showed that the risk is increased most in those who are placed at the window seat or who travel economy class. In our case-crossover study (**chapter 3**), TAT levels decreased by 2.1% after immobilisation in a cinema, whereas TAT levels increased after the 8-h flight (30.1%, CI95: 11.2 to 63.2). Also, we noted a high response in only 3% (CI95: 0.4 to 10.2) of the volunteers after immobilisation in the cinema while the flight caused a high response in 17% (CI95: 8.6 to 27.9) of the individuals. So, it seems that there is more to the mechanism of air travel related thrombosis than immobilisation alone. In any case, immobilisation does not explain the clotting activation that we found after the 8-h flight.

Dehydration. Although fluid loss (or dehydration) is not an established risk factor for venous thrombosis, it is often believed that the low humidity, which can be as low as 10% in long haul flights (20), contributes to the development of thrombosis through fluid loss. This idea is probably reinforced by the sensation of dry eyes and dry skin during air travel. In general, there is no evidence for the hypothesis that exposure to a low humidity environment per se can lead to dehydration (21). The few studies that focused on fluid loss during either real or simulated air travel showed conflicting results. Some found evidence for fluid loss (22-25), while others did not (26-29). Results of studies into the effect of immobilisation on parameters of dehydration were also inconclusive (30-33). In our case-crossover study (**chapter 4**), we compared changes in hydration state between volunteers with and without an activated coagulation system and found no difference. Also, we found no relationship between hydration parameters and TAT, F1+2 and D-dimer. Therefore, we concluded that our results do not support the hypothesis that changes in hydration level trigger coagulation activation. This is in line with the results of our case-control study (**chapter 7**) in which we found no effect of copious intake of non-alcoholic drinks on the risk of venous thrombosis after air travel (OR 1.1; CI95: 0.3 to 3.8). So, although it is not clear whether fluid loss occurs during air travel, fluid loss does not explain the coagulation activation that we found in 17% of the volunteers after air travel.

Stress. Individuals who are afraid of flying can experience anxiety during air travel. Stress is known to increase levels of several coagulation parameters, such as von Willebrand factor and clotting factor VIII (34). Therefore, it has been suggested that stress could underlie air travel related thrombosis. In **chapter 7** we reported that self-reported stress increased the risk of venous thrombosis after air travel 2.5 fold in a case-control setting. In our case-crossover study, volunteers with clotting activation after the flight were not more anxious than others (**chapter 6**). Factor VIII increased more in volunteers with clotting activation than in volunteers without coagulation activation. However, this was not related to anxiety experienced during the flight. So, there seems to be no direct effect of stress on coagulation activation in our study. Still, we have to be cautious with interpreting these results since the levels of stress experienced during the flight were not very high, probably because people who are afraid of flying do not volunteer for a research project such as ours.

Hypoxia. During air travel, cabin pressure drops to 75.8 kPa, which is equivalent to an altitude of 2400 m above sea level. Consequently, oxygen saturation can drop as low as 90–93%, and even to 80% in passengers who are asleep (23;35), which may even cause acute mountain sickness (36). In **chapter 2**, we reviewed studies into the effect of both hypobaric as well as normobaric hypoxia on human

coagulation (37). Most controlled experiments found no effect of either 8 h of isocapnic hypoxia (14), short-term normobaric hypoxia (38) or 8 to 10 h of hypobaric hypoxia (11) compared to normobaric normoxia. One drawback of these studies is that participants with risk factors for venous thrombosis were not included (**chapter 2**).

A parameter that is sensitive for hypoxia is PAI-1, one of the inhibitors of the fibrinolytic system (39). Previous research found an increase of PAI-1 during air travel (28). Several hypobaric chamber studies found no effect of hypoxia on PAI-1 (11;29;38). In our study PAI-1 increased during the flight in individuals with an activated clotting system whereas it decreased in those without coagulation activation. Furthermore, out of the 11 subjects with clotting activation, 6 were also high responders in PAI-1. Levels of PAI-1 after the flight were related to levels of sP-selectin. So, there seems to be role for hypoxia in the mechanism underlying coagulation activation after air travel (**chapter 6**).

Air pollution. We wondered whether air pollution could play a role. Around airports, the air is polluted by aviation fuels and their combustion products. Aircraft emissions vary with engine type, engine load and kind of fuel. Combustion of aviation fuels results in CO_2, CO, C_e, NO_x, particles, and a great number of other organic compounds, among which a number of carcinogens (40;41). For this purpose, we investigated changes in neutrophil elastase. Although neutrophil elastase did not differ between the two groups, we did find a relationship between absolute changes in neutrophil elastase levels and levels of sP-selectin after the flight situation. This supports the theory that inflammation could play a role in platelet activation during air travel, but not in coagulation activation directly (**chapter 6**).

Infection. We hypothesised whether passengers could be more at risk for infection, since they are placed in a small cabin for a long time during air travel, allowing germs to spread. Inflammation and thrombosis are related via interactions between leucocytes, platelets, the vasculature and the coagulation pathway (42;43). Results from a self-controlled case-series method in a large cohort study showed that acute infections are associated with a transient increased risk of venous thrombosis in a community setting (44). To study whether an infection was present, or occurred during the flight, that triggered the coagulation activation, we measured IL-8 in the participants of the cross-over study. We found no difference in levels of IL-8 between individuals with and without coagulation activation after the flight, indicating that an effect of infection on clotting activation after air travel is unlikely (**chapter 6**).

Platelets and the vessel wall. The effect of air travel on platelets and the vessel wall is not well understood. Therefore, we measured platelet number, markers of platelet activation (sP-selectin, ß-thromboglobulin) and endothelial

activation (sE-selectin, von Willebrand factor) in our case cross-over study (**chapter 5**). We found that air travel led to a moderate level of platelet activation, but it did not seem to affect the vessel wall. Also, changes in P-selectin were related to changes in TAT, indicating a direct relationship with thrombin formation in these volunteers.

Effect of behaviour of passengers. In a case control setting (**chapter 7**), we studied the effect of behaviour during air travel on the risk of venous thrombosis after air travel. We also looked for evidence to support the so called 'common sense' advice that is given by physicians and airlines to reduce the risk of venous thrombosis, i.e., to avoid alcohol, to drink water and exercise regularly during air travel. We found that window seating increased the risk 2-fold, and even 6-fold in those who were obese. Anxiety and sleeping were associated with a slight increase in risk. The risk was not affected by drinking of alcoholic beverages. Flying business class seemed to lower the risk. We did not find a protective effect for several standard preventive measures, i.e. copious drinking of non-alcoholic beverages, exercising or wearing stockings. So, in conclusion, several behavioural aspects seem to affect the risk of venous thrombosis after air travel. Current advice on prevention of thrombosis after air travel may need to be reconsidered.

Prevention methods for venous thrombosis after air travel (chapter 8). As mentioned before, the effect of preventive methods of venous thrombosis after air travel is poorly investigated. We investigated the effect of relatively harmless prevention methods (i.e. exercise, a calf muscle pump and elastic stockings) on popliteal vein flow velocity, changes in lower extremity volume and fibrinolytic activity during 8 hours of immobilisation in a small case crossover study. The results suggested that each of the interventions improves a different outcome measurement, while none of the interventions was able to improve all three.

In conclusion, the results in this thesis show that immobilisation alone does not explain coagulation activation after air travel. A factor that seems to contribute is hypoxia. The results do not support the theories that fluid loss, air pollution, infection or stress play a role in coagulation activation after air travel. Certain kinds of behaviour during air travel affect the risk of venous thrombosis. Lastly, harmless prevention methods (e.g. exercise, muscle pumps, stockings) possibly counter the effect of immobilisation, but their efficacy needs to be further investigated in large scale studies.

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