'Traveller's Thrombosis' – Does It Exist and Are We Ready to Give Prophylaxis?

a report by

Frits R Rosendaal

Chairman, Departments of Clinical Epidemiology and Thrombosis and Haemostasis, Leiden University Medical Centre

DOI: 10.17925/EOH.2007.0.0.50

In June 2007, the World Health Organization (WHO) released its report on air travel and thrombosis, summarising the results of the WHO Research Into Global Hazards of Travel (WRIGHT) project.[1]

Venous Thrombosis

The incidence of venous thrombosis, which manifests mainly as deep vein thrombosis (DVT) of the leg and pulmonary embolism (PE), is around two per 1,000 per year. Venous thrombosis is a serious disorder. In the acute phase, 6% of patients die, while after one year >20% die.[2] Of those who survive, up to 25% of patients develop a chronic post-thrombotic syndrome due to venous insufficiency. Causes of venous thrombosis can be genetic or acquired and are related to either immobilisation or hypercoagulability.[3] Major risk factors are surgery, pregnancy, puerperium, cancer, deficiencies of the natural anticoagulants protein C, protein S and antithrombin and mutations in procoagulant factor II and factor V (factor V Leiden). Immobilisation has been known to increase the risk of thrombosis for centuries. Virchow recognised stasis as a risk factor in the mid-1800s. In the 1930s, thrombosis was reported after long car journeys, during World War II it was seen after prolonged hiding in cramped conditions in the London Underground[4] and in the 1950s the first cases of thrombosis after air travel were reported.[5] Modern forms of thrombosis related to immobilisation include reports of its occurrence after major traffic jams and prolonged computer use for work or playing computer games.[6,7] Venous thrombosis after air travel was coined 'economy class syndrome' in the 1970s,[8] but it took until the late 1990s before the first controlled studies were published. These were generally small, and while some showed an increased risk, others did not (reviewed by Kuipers et al.[9]). An additional putative risk factor specific to air travel was suggested in 2000, when it was shown in a volunteer study that low air pressure, and hence low oxygen, may lead to activation of the coagulation system.[10]

The World Health Organization Research Into Global Hazards of Travel

To estimate the absolute risk (probability) of thrombosis after air travel, nearly 9,000 employees from international organisations were followed over a period of five years.[11] During this time they caught over 100,000 flights lasting more than four hours, and 53 confirmed DVTs and PEs occurred. This led to a risk estimate (probability) of one per 4,656 travellers (95% confidence interval [CI95] 1/7,526–1/3,163) (see *Table 1*, adapted from Kuipers et al.[11]). During an eight-week time window after a long-haul flight, the risk of thrombosis increased 3.2-fold compared with other time periods. The risk of thrombosis rose sharply with the duration of the flight to one per 1,200 travellers for flights over 16 hours. Those who made several flights within the eight-week time window also had increased risks. Furthermore, the risk was increased in women, particularly in oral contraceptive users, and in those who were obese, tall or short. So, although the overall risk was not very high, there are risk groups with a clearly increased risk that may become substantial in those with multiple risk factors. Subsequently, a case-control study was performed among 1,906 patients with a first DVT or PE and 1,906 controls.[12] Due to the larger number of cases in a case-control study than in a follow-up study, this design allows for in-depth analysis of contributing risk factors but yields only relative risks and not absolute risks. Travelling for more than four hours increased the risk of thrombosis two-fold (CI95 1.5–3.0) and did so regardless of the mode of travel, i.e. by plane, car, bus or train. Again, the risk was highest for the journeys with the longest duration. The risk of thrombosis was further increased for those who were obese, tall or short. The latter two are remarkable, as they do not increase the risk of thrombosis in the absence of travelling. Most notable is the risk associated with travel for short people, as this was restricted to air travel and was not observed for other modes of travel. In this study, blood samples were drawn and prothrombotic mutations were determined, i.e. factor V Leiden and prothrombin mutation 20210A. These abnormalities are common in the general Caucasian population, and in the absence of travel increased risk three-fold. Relative risks were higher after travel, particularly air travel, with eight- to 14-fold increased risks (relative to those without mutations who did not travel).

Frits R Rosendaal is Professor of Clinical Epidemiology at the Leiden University Medical Centre in The Netherlands, where he chairs the Departments of Clinical Epidemiology and Thrombosis and Haemostasis. He is President of the Netherlands Society for Thrombosis and Haemostasis, Secretary/Chairman of the Council of the International Society for Thrombosis and Haemostasis (ISTH) and Associate Editor of the *Journal of Thrombosis and Haemostasis*. He studied medicine in Rotterdam and obtained his PhD at Leiden University.

E: f.r.rosendaal@lumc.nl

Does 'Traveller's Thrombosis' Exist?

From the WRIGHT studies it has become clear that the risk of thrombosis is increased after air travel, with an average risk of around one per 4,500 travellers. Due to the large size of the studies, the risk estimate of a two- to three-fold increased risk is highly precise, and it was concordant even between studies with very different designs. There are no plausible alternative explanations and so the conclusion that air travel causes thrombosis is justified. Whether one calls this affliction 'traveller's thrombosis' or 'economy class syndrome' is a matter of taste. Although the risk may well be higher in economy than business class, thrombosis does occur in both. In most named diseases (e.g. 'miner's lung') there is a one-to-one relation between the exposure and the risk factor, almost to the extent that the disease will invariably occur in the presence, and never in the absence, of the risk factor. This is far from the case for thrombosis after air travel, or for any other risk factor for thrombosis, as it is a multicausal disease.[3] Venous thrombosis occurs due to a specific set of risk factors that are present

© TOUCH BRIEFINGS 2007

simultaneously in an individual; each of these factors affects the probability of disease. Hence, the term 'traveller's thrombosis' is as inappropriate as 'cholesterol myocardial infarction' or 'smoker's stroke' would be.

Preventing Venous Thrombosis After Air Travel

There are no studies concerning the prevention of thrombosis after air travel. There are guidelines, sometimes referred to as 'common sense advice', that include avoidance of alcohol, liberal intake of non-alcoholic beverages and regular exercise of the legs. It is not very likely that dehydration plays a role in the development of thrombosis, but it is plausible that regular movement of the legs will be beneficial. Exercise is obviously also without a risk of side effects, but this is not the case for other suggested prophylactic measures, such as elastic stockings, aspirin and low-molecular-weight heparin. A recent survey of physicians travelling to Australia showed that many used aspirin before the flight.[13] The effect of aspirin on thrombosis occurrence is minimal, but it does increase the risk of major haemorrhage. Elastic stockings prevent oedema and have been shown in other risk situations to decrease thrombotic risk. It is, from a biological viewpoint, unlikely that stockings have much effect in the absence of leg muscle movement. Several studies focusing on asymptomatic clots detected by ultrasound observed a decrease in the number of such clots occurring in those wearing elastic stockings, but in one study grade I elastic stockings caused symptomatic superficial thrombosis in 3% of patients.[14] Therefore, elastic stockings are not without potential side effects. Elastic stockings should exert a pressure that is graded from distal to proximal, and should be individually tailored. It is highly implausible that the 'one-size-fits-all' socks that are sold over the counter at airports have any effect in preventing thrombosis. Low-molecular-weight heparin has proved to be highly effective in many situations to prevent thrombosis, but also clearly increases the risk of major haemorrhage.

In the absence of data on prophylaxis of thrombosis after air travel, we can only try to extrapolate from existing data. The potential benefit is determined by the magnitude of the risk and the efficacy of the intervention, and can be expressed as the number needed to treat (NNT) and number needed to harm (NNH). NNT is the number of individuals one has to treat to prevent one thrombotic event and NNH is the number one treats before causing a major haemorrhage. When prophylaxis is given indiscriminately to all travellers and the treatment is completely efficacious, 4,656 travellers needed to be treated to prevent one thrombosis (NNT). Aspirin is far from perfectly efficacious, and reduces risk by, at most, 25%. Hence, with aspirin one would need to treat 18,000 travellers to prevent one thrombotic event. Heparin reduces risk more efficiently and with a risk reduction of 70%, and NNT for heparin is still nearly 7,000. The NNT for elastic stockings is unknown, and may lie somewhere between the region of 7,000 and 18,000 travellers wearing them in order to prevent one case of thrombosis. The benefits of these interventions do not outweigh the risks of either thrombosis inducement (stockings) or major haemorrhage (aspirin, heparin). Risks of major haemorrhage for short-term use of aspirin and heparin are low, but may outweigh the equally small benefit. For instance, for aspirin the risk of major haemorrhage in healthy users would be one per 17,000 travellers, and for low-molecular-weight heparin one in 3,500.[15] This implies that prophylaxis with stockings, aspirin or heparin in all travellers is not indicated. These figures, particularly NNT, will be different for individuals with risk factors; however, given the substantial uncertainty concerning the estimates of benefit and harm and the absence of data, caution is needed in prescribing any prophylaxis beyond exercise.

Table 1: Absolute and Relative Risks After Long-haul Flights for the Whole Study Population as Well as Stratified by Sex, Age Category, Oral Contraceptive Use, Height and Body Mass Index

Category (n)	Air Travel	Flights (n)	Case/Number of Travellers ###	## RR (CI95)
All (8,755)	No			1$
	Yes	102,429	4,656	3.2 (1.8–5.6)
Men (4,915)	No			1$
	Yes	76,461	5,882	2.7 (1.2–6.0)
Women (3,819)	No			1$
	Yes	25,780	2,864	3.3 (1.5–7.5)
<30 years (1,392)	No			1$
	Yes	8,014	2,671	7.7 (1.6–38.4)
30–50 years (6,017)	No			1$
	Yes	73,624	4,908	3.7 (1.8–7.5)
>50 years (1,345)	No			1$
	Yes	20,791	5,198	1.4 (0.4–4.6)
OC$$ No	No			1$
	Yes	18,085	4,938	2.2 (0.6–8.1)
OC$$ Yes	No			1$
	Yes	7,695	1,808	3.6 (0.8–14.9)
<165cm	No			1$
	Yes	14,250	2,036	9.8 (3.1–30.9)
165–185cm	No			1$
	Yes	69,095	6,281	1.9 (0.9–3.9)
>185cm	No			1$
	Yes	18,242	4,561	3.7 (0.8–16.9)
BMI <25	No			1$
	Yes	51,958	7,423	1.9 (0.8–4.7)
BMI>25	No			1$
	Yes	49,509	3,301	4.9 (2.3–10.6)

No = no exposure to air travel within 8 weeks; Yes = exposure to a flight of at least four hours; ## RR = relative risk, adjusted for age and sex with 95% confidence interval (CI95); $ = reference category; $$ = oral contraceptive use among women <50 years of age; ### = number of travellers (flights) among whom one case will occur.

Conclusion

Air travel increases the risk of thrombosis, with an average risk of one per 4,500 travellers. Long flights, as well as several flights in quick succession, lead to higher risks, as does the presence of risk factors such as obesity, being tall or short, use of oral contraceptives and prothrombotic mutations. Current data, which are limited, do not favour prescription of prophylactic interventions such as aspirin, low-molecular-weight heparin or elastic stockings and prevention should be limited to encouraging exercise and discouraging behaviour that will restrict movement, such as excessive alcohol intake and the use of sleeping medication. There is a need for studies into the efficacy and safety of preventative measures in high-risk individuals. ■

1. World Health Organization (WHO) Research Into Global Hazards of Travel (WRIGHT) project: Final Report of Phase I, 2007.
2. Naess IA, Christiansen SC, Romundstad P, et al., *J Thromb Haemost*, 2007;5:692–9.
3. Rosendaal FR, *Lancet*, 1999;353:1167–73.
4. Simpson K, *Lancet*, 1940;2:744.
5. Louvel J, Four cases of phlebitis due to air travel, *Arch Mal Coeur Vaiss*, 1951;44:748–9.
6. Eschwège V, Robert A, *Lancet*, 1996;347:206.
7. Beasley R, Raymond N, Hill S, et al., *Eur Respir J*, 2003;21:374–6.
8. Symington IS, Stack BHR, *Br J Dis Chest*, 1977;71:138–40.
9. Kuipers S, Schreijer AJM, et al., *J Intern Med*, 2007; in press.
10. Bendz B, Rostrup M, Sevre K, et al., *Lancet*, 2000;356:1657–8.
11. Kuipers S, Cannegieter SC, Middeldorp S, et al., *PLoS Med*, 2007;4:290.
12. Cannegieter SC, Doggen CJM, van Houwelingen HC, *PLoS Med*, 2006;3(8).
13. Kuipers S, Cannegieter SC, Middeldorp S, et al., *J Thromb Haemost*, 2006;4:2373–6.
14. Scurr JH, Machin SJ, Bailey-King S, et al., *Lancet*, 2001;357:1485–9.
15. Rosendaal FR, *J Thromb Haemost*, 2006;4:2306–7.