



REVIEW

Travel and thrombosis

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KEYWORDS

Deep vein thrombosis;
Pulmonary embolism;
Economy class
syndrome;
Travel;
Risk factor;
Prophylaxis

Summary The available evidence suggests an association between long distance travel and the development of venous thromboembolism. The main problem for travellers and physicians is the interpretation of the evidence and its translation into appropriate advice on the risk and the prevention of thrombosis. Most available data relate to air travel. Thrombosis risk is greater following journeys of more than 8 h and those at greatest risk are travellers with a history of venous thromboembolism or risk factors. Based on the best evidence available the risk of symptomatic venous thromboembolism after flights of more than 12 h is 0.5%. It is likely that stasis plays a major role in the aetiology of travel related thrombosis. The evidence for hypobaric hypoxia induced coagulation activation requires confirmation. There is evidence that compression stockings and low molecular weight heparin prevent asymptomatic deep vein thrombosis (DVT) but clinical DVT has been observed in long distance flyers in spite of prophylaxis with aspirin and stockings.

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Introduction

Many factors have contributed to the state of "thrombosis neurosis" which now prevails in many western countries. The excellent work which led to the description of activated protein C resistance,¹ and the subsequent discovery of the factor V Leiden mutation, which accounts for the vast majority of inherited causes of this state in Northern Europeans,² was unfortunately followed by a proliferation of poorly designed small, misleading studies, a frenzy of inappropriate patient and family screening and the development of non-evidence based practices, which have persisted in spite of the

availability of studies and guidelines which do inform on appropriate practice.^{3,4} Furthermore, the popular media have ensured that whenever studies that describe an increased thrombosis risk, related for example to the use of female sex hormones, are reported it is done in such a sensationalist way that pill takers take fright, lapse and unwanted pregnancies result. The coverage of travel associated thrombosis has been similar and in the aftermath of the unfortunate and untimely death of a young British woman in 2001⁵ reporting has often given a sensationalist and biased account of the problem. As a result most people, including doctors, now believe that venous thromboembolism (VTE) is a common complication of travel. Because the high profile cases that have been reported in the media are more often associated with air travel it is

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perceived that this form of travel poses the greatest threat. The author is frequently asked by prospective air travellers (even those embarking on relatively short flights) for advice on prevention of deep vein thrombosis (DVT), but has yet to be asked for counselling about risk of thrombosis by anyone travelling for much longer periods by road or rail. The evidence that is available suggests that there is a weak association between travel and thrombosis but that as in most cases of thrombosis the pathogenesis is multifactorial. Because long distance travel is so common and concern so great for the reasons mentioned above, it is important that we delineate the risks of thrombosis associated with travel and provide appropriate advice for travellers to allow them to make informed, evidence based decisions on the adoption of appropriate preventative measures. At present, some guidance on risk and prevention of thrombosis is available^{6,7} but it is clear from the sales of compression stockings and the reported use of aspirin that large numbers of travellers are probably adopting prophylactic measures unnecessarily. Many people, including some medical practitioners wrongly believe that doing something positive like taking or recommending aspirin is only ever beneficial. This is all very well where an intervention has been properly assessed and a comparison of its benefits and complications made. However inappropriate extrapolation of recommendations, for example on the use of aspirin, could potentially result in serious consequences such as gastrointestinal bleeding or even Reyes syndrome if a travelling adult decided to give a small child a dose "just to be safe".⁸

In this review I will assess the relationship between travel and thrombosis, discuss the possible mechanisms underlying any association and review the evidence for prevention of thromboembolism in travellers.

Early observations and associations

The first report of VTE during or soon after prolonged travel was probably made in 1954.⁹ In his report, Homans drew attention to an earlier suggestion that cramped overnight sitting in crowded underground stations during the Second World War may have been associated with an increased risk of the development of fatal pulmonary embolism.¹⁰ Both Homans and Simpson considered that prolonged stasis of blood in the deep veins of the legs may have contributed significantly. This conclusion is in fitting with the hypothesis of

Virchow and indeed in modern medicine prolonged immobility is generally accepted as being a risk factor for the development of VTE. Based on these early findings alone there would appear to be a rationale for prolonged travel being associated with the development of venous thrombosis. What was not clear was the magnitude of the risk and whether any other specific factors were contributing to the risk.

Venous thromboembolism is a relatively common disorder with an incidence of around 1 per 1000 per annum. In about half of all cases, there is a clear underlying acquired predisposing factor which may be temporary or permanent. It is clear that VTE is a multicausal disorder and that in many cases it is the co-occurrence of two or more risk factors at one time that results in the development of the clinical condition.¹¹ It has been suggested that the association of venous thromboembolism with prolonged travel merely reflects the chance association of two prevalent events.¹² Simple calculations indicate that based on an incidence of DVT for the whole population of 1 per 1000 per annum, one would expect to see one DVT develop in any 8-h period in 1 in a million people. The chance of developing a DVT over a period of 4 weeks is around 1 in 10,000. Therefore at the end of an 8-h period of travel, having embarked without a DVT one in a million people would be expected to have developed a DVT. It is common however to ascribe DVT to prolonged travel which occurred as long as 4 weeks prior to presentation. If this is done then the chance of the DVT having developed without any additional risk associated with travel is significantly higher at 1 in 10,000. This needs to be borne in mind when interpreting the data that are presented. Other data that indicate that some caution is required in ascribing thrombosis risk to prolonged travel come from an Australian study in which the pathological features of what were deemed to be fatal pulmonary emboli, in travellers with "economy class syndrome", were examined in detail in order to "age" the clots. The investigators assessed the age of thrombi using parameters such as macrophage content, fibroblast invasion, organisation and evidence of vessel recanalisation to decide whether the clots had occurred subsequent to or before the implicated long distance flight. Of 14 cases, it was concluded that four "fatal pulmonary emboli" had occurred prior to the travellers embarking on the implicated flights.¹³

Finally, several cases have been described where the risk factor for development of thrombosis has been attributed to sedentary behaviour, independent of travel.¹⁴ These observations may indeed take us full circle and concord with

Simpson's observation that the main risk associated with travel is indeed stasis.

The evidence that travel is associated with a thrombosis risk

Studies of severe pulmonary embolism very soon after air travel

Of all the data which are available these provide the most compelling evidence of both a link between air travel and thrombosis and of an association between the duration of travel and the thrombosis risk. Three similar studies, two from France and one from Spain have used the data from emergency referral centres near to large airports to document the incidence and associations of severe pulmonary embolism (PE) occurring very soon after flights.^{15–17} The compelling features of these reports in comparison to other studies are that they document the characteristics of a group of patients with severe symptomatic pulmonary embolism which was objectively diagnosed in each case. Further the history of travel is very recent and robust unlike much of the data from case control studies in which recall is almost certainly biased by the widely held belief that travel is a very common cause of thrombosis. Each of the studies looked retrospectively at all cases of severe symptomatic pulmonary embolism presenting within an hour of disembarkation. In each case small numbers of confirmed cases were reported (136 in total). Two main conclusions arose from each study. Firstly, the majority of travellers who develop severe PE have pre-existing thrombotic risk and secondly the risk of severe PE is clearly related to the duration of travel. In the study of Clerel et al., 31% of the passengers who sustained severe PE had other predisposing factors for thrombosis. Seven percent and 78% of cases reported by Lapostolle had high or moderate pre-existing risk for thrombosis development and 56% of the cases reported by Perez-Rodriguez had one risk factor for thrombosis while 44% had two (Table 2). These findings are very much

in fitting with general perception of thrombosis risk in other situations. All three studies also reported a strong relationship between the duration of travel and thrombosis risk. Clerel reported that 76.5% of cases had travelled for more than 12 h, while in the study of Lapostolle 82% had travelled for longer than 9 h and in the Spanish study 93.7% had travelled for more than 8 h. The risk of severe PE reported by the two French studies was remarkably similar at 4.77 and 4.83 per million for flights over 12 h long. The Spanish study meanwhile reported a rate of 1.65 per million for flights of greater than 8 h which is similar to the rate of events for flights over 8 h in the Lapostolle study. In comparison the rate of severe PE for all travellers independent of distance was 0.5, 0.39 and 0.41 per million and the incidence following journeys of less than 6 h zero and 1 in 97.7 million, respectively.^{16,17} Overall, the results of these studies are not only very similar but they are also in fitting with our pre-existing understanding of the risks and associations of VTE (Table 1).

Case control studies of recent travel and venous thromboembolism

A number of case-control studies have been carried out to investigate the prevalence of recent travel in cases with VTE compared with controls without VTE. In addition, one prospective study has been specifically designed to identify the risk factors for thrombosis development in long distance flyers who developed VTE compared to fellow travellers who did not.¹⁸ There are of course difficulties in comparing these studies because of the varying methodologies and recruitment. For example in two studies, the cases were consecutive patients with a diagnosis of VTE while the controls were patients seen for other reasons but not for suspected VTE.^{19,20} In three other studies, the cases and controls were all patients with clinically suspected VTE. In these reports, the controls consisted of those from the initial patient group who were shown not to have thrombosis.^{21–23} In a further study, the cases were of patients with a history

Table 1 Summary of studies of severe pulmonary embolism occurring soon after flight.

	Clerel ¹⁵	Lapostolle ¹⁶	Perez-Rodriguez ¹⁷
Passenger number total		135.3 million	41 million
Cases of severe PE	64	56	16
Predisposing factors	31% any	High risk 7%, moderate risk 87%	One risk factor 56%, two risk factors 44%
Severe PE rate	4.83 per 10 ⁶ for flight >12 h	4.77 per 10 ⁶ for flight >12 h	1.65 per 10 ⁶ for flight >8 h

Table 2 Presence of risk factors for thrombotic in cases (and controls).

Study	Thrombotic outcome	Risk travellers (%)
Lapostolle ¹⁶	Severe pulmonary embolism	7% high, 87% moderate
Perez-Rodriguez ¹⁷	Early pulmonary embolism	56% one risk factor, 44% two risk factor
Clerehugh ¹⁵	Early pulmonary embolism	31% increased risk
Paganin ¹⁸	Symptomatic DVT, PE	82% risk factor for thrombosis
Martinelli ²⁴	Symptomatic first VTE	Cases: controls OCP: 61%:27% Thrombophilia 49%:12% All risks 52%:4%
Hughes ³² (NZATT)	DVT or PE (>50% symptomatic)	6/9 (67%) pre-existing risk factors Thrombophilia 22% cases; 8% controls

of confirmed VTE who were attending a specialist thrombosis centre for thrombophilia testing while the controls were their friends and family.²⁴ The potential flaws in the design of studies where the control group are derived from the initial study group by exclusion of the diagnosis have been discussed.²⁵ The use of patients deemed to require thrombophilia screening in the Italian study almost certainly produces a bias by including an excess of young otherwise fit patients without other obvious risk factors for thrombosis.²⁴

Another variable in these studies is the definition of long distance travel as a risk factor in terms of its duration and its proximity to the episode of thrombosis. Some studies included journeys of more than 3 h,^{21,22} while others considered journeys of greater than 4 h¹⁹ or of a mean of 2 h.²⁴ Finally, the studies are all heavily dependent on the recall of the subjects. As such the prevalent notion that travel is a common cause of VTE would be expected to bias the responses of those subjects with VTE. Interestingly in one study the case group included patients who had sustained the episode of thrombosis in question up to 24 months prior to inclusion.²⁴

Three studies show an effect of travel on thrombosis risk with odds ratios of 2.1–3.98^{19,20,24} while others show no effect.^{21,22} In one study, an effect of travel was not observed for all travel of greater than 3 h but was observed in patients who had travelled for more than 10 h.²³

Prospective studies of the incidence of venous thromboembolism after travel

Several studies have prospectively identified flyers prior to travel, excluded evidence of active thrombosis and then reassessed them on their return by a variety of methods to confirm or exclude thromboembolism. In addition to giving rates of thrombosis some have assessed different forms of intervention to prevent VTE. If we ignore the risk categories for

the travellers and the prophylactic interventions the reported rate of thrombosis development is between 0% and 5.1%.^{26,27} Among individuals travelling without any attempt at prophylaxis, the rate of thrombosis ranges from 0% to 10%.^{26,27} If we exclude the Scurr study, which does appear to be at odds with other reported rates of thrombosis, then in individuals without prophylaxis, rates of VTE of 0%, 2.5%, 2.82%, 4.5% and 4.82% were observed.^{26,28–30} In all of these studies, the flight duration was greater than 8 h and in all cases objective methods were used to diagnose thrombosis. However, a serious weakness in all but one study is that the entity which was diagnosed was predominantly asymptomatic DVT involving only the calf veins. The natural history of asymptomatic calf vein thrombosis diagnosed soon after long distance travel is not known – and few of the studies gave any follow-up information on the development of symptoms. The significance of these findings is highlighted by one study where six of 12 flyers in whom thrombosis was observed had no elevation of D-dimers.²⁷ Under normal clinical circumstances, patients with a low thrombosis risk score and a negative D-dimer test are excluded from further investigation with a high negative predictive value.³¹ In the NZATT study 5/9 (56%) of the travellers with DVT and 3/8 (38%) of those with PE were symptomatic. It is worth noting however that among non-affected travellers in the same study 33% and 10% reported symptoms of DVT and PE, respectively.³²

Finally, the prospective studies again confirm that the risk of thrombosis is higher in groups of individuals with pre-existing risk factors. In studies of low risk individuals the rate of thrombosis is extremely low. Jacobson and colleagues reported no episode of thrombosis following 11 h of flying in a group that excluded high risk patients, while in LONFLIT 1 thrombosis was seen in 11/389 (2.82%) individuals with pre-existing risk factors such as previous DVT, documented coagulation abnormal-

ity, severe obesity, limited mobility due to bone and joint problems, recent neoplastic disease and large varicose veins compared with no episodes in 355 flyers without these problems.²⁸ One other risk factor which appears to be significant in these studies is the seating arrangement. In the LONFLIT studies between 85% and 100% of observed asymptomatic DVTs developed in patients occupying window or central seats as opposed to aisle seats.^{28,29}

In summary, these studies do suggest that clot formation is associated with long distance travel by air. Outwith the NZATT study however where up to 56% of events were symptomatic it is difficult to interpret the data other than to say that it supports a causal association between venous thrombosis and air travel. The NZATT study was however well conducted and reported and it does suggest an incidence of symptomatic venous thromboembolism of around 0.5% for journeys of greater than 12 h.

Possible mechanisms contributing to prothrombotic tendency

While most of the published data relate to the risk of thromboembolism after air travel, there are data from large studies that suggest an equal risk exists for travel by other modes.^{19,33} If this is indeed the case then the candidate mechanism which is common to all forms of travel is stasis. Of course stasis is a common feature of many activities and as mentioned earlier, stasis without horizontal or vertical travel has been implicated in other episodes of VTE.¹⁴ Is it possible that stasis alone could produce this effect? Sitting for as little as 1 h reduces venous return from the legs and leads to local haemoconcentration^{34,35} and 12 h simulated air travel results in swelling and fluid retention.³⁶ These changes might be expected to confer a thrombosis risk. Evidence from recent reports which indicate that 85–100% of VTE occur in passengers in non-aisle seats^{28,29} and that 42 of 45 travellers with severe PE did not leave their seats adds weight to the association of stasis with thrombosis although the later report is likely to be biased by the perception of the crowded economy class syndrome.¹⁶

Because most attention has focused on air travel and thrombosis, it has been suggested that in addition to the effects of stasis, cabin conditions may contribute to the apparent prothrombotic tendency. Hypobaric hypoxia is a feature on pressurised commercial aircraft. The air pressure is dependent on the length of the flight and the type of craft and corresponds to the air pressure 1800–2400 m above sea level. Several studies have reported on the effects on the coagulation system

of both hypoxia and hypobaric hypoxia. In two studies in which normobaric hypoxia was induced in normal volunteers for 3–8 h, no evidence of coagulation activation, as measured by generation of prothrombin fragments 1 and 2 (F1 + 2), thrombin-antithrombin complexes (TAT), d-dimers, soluble p-selectin or fibrinogen was observed.^{37,38} On the other hand during an 8-h exposure to hypobaric hypoxia at 76 kPa, thrombin activation as indicated by changes in F1 + 2 and TAT was observed.³⁹ Interestingly the maximum changes were seen after only 2 h exposure. Whereas these studies took place in a simulator, Schobersberger and colleagues have recently recorded significant falls in APTT, and levels of tissue plasminogen activator (tPA), alongside a rise in plasminogen activator inhibitor-1 (PAI-1) in a group of low and moderate risk volunteers following a transatlantic flight.⁴⁰ These suggest inhibition of fibrinolysis while in the same group activation of coagulation was not observed.

There are no data that suggest that hypoxia alone induces significant coagulation activation. The information from studies of hypobaric hypoxia is presently inconclusive. The Bendz data are unusual in that the volunteers had inexplicably high levels of markers of coagulation activation prior to exposure to hypobaric hypoxia. Presently, other groups are having difficulty reproducing these observations in much larger studies. Further, only limited conclusions can be drawn from these data because of the lack of controls.

One cabin condition above all others is perceived as conferring a high risk of thrombosis – economy class seating. Is this the case however? In considering these data it is appropriate to remember that on most planes around 10% of seats are business class. In Cheung and Duflo's autopsy study of 14 fatal PE, 2 (14%) arose in business class.¹³ Business class PE represented 15% and 19% of all cases in two other studies suggesting that the title economy class syndrome is indeed a misnomer.^{18,24}

Prevention of VTE during travel

An increasingly prevalent question being asked of clinicians relates to risk of travel associated thrombosis and the need for and nature of appropriate thromboprophylaxis. In order to make any recommendation of this sort it is appropriate to consider the risk of thrombosis, the evidence for a benefit of the proposed action, and the likelihood of side effects. In some respects, the public have already come to their own conclusions and made their decisions. Thus in the NZATT study, use of aspirin and stockings was recorded in 56% and 44% of travellers

who developed thrombosis and 31% and 16%, respectively, of those who did not. This is surprising given that there are few good data to support the use of aspirin for venous thromboembolism prophylaxis^{29,41} and that the use of compression stockings has been implicated as a risk factor for development of superficial thrombophlebitis during travel.²⁷ These findings are however testimony to the belief that treatment can only be a good thing.

Several studies have assessed the benefit of interventions which might be expected to reduce the risk of thrombosis. Again in each of the studies the end point is asymptomatic DVT and although this might be a reasonable surrogate marker of clinical DVT, it does limit interpretation somewhat. Compression stockings have been assessed in two studies involving 1064 flyers.^{27,28} Thrombosis rates in the controls were 4.5% and 10% compared with 0.24% and zero in stocking wearers. In the LONFLIT 2 study the subjects were all "high risk" and the comparison was in fact of stockings plus general measures which the travellers had been asked to undertake including stretching, taking adequate fluids and moving around the cabin for 3 min per hour. In a study of 249 "high risk" travellers comparing no intervention with the prophylactic effects of 400 mg aspirin for 3 days, or with a single dose of low molecular weight heparin (10 mg per 10 kg), the respective rates of asymptomatic thrombosis were 4.82%, 3.6%, and 0%. The outcome for the heparin group was significantly different from the others ($p < 0.05$).

Although there are no data indicating the efficacy of "Flite tabs" in prophylaxis of VTE, a study on the use of this drug has been completed in travellers. "Flite tabs" contain pinokinase, a profibrinolytic drug and also a component that controls oedema. No episode of thrombosis was recorded after 7–8 h flights in "Flite tab" recipients and on an intention to treat analysis a significant benefit for "Flite tabs" was demonstrated; 18 (19.6%) treatment failures versus 7 (7.4%) $p < 0.05$. No side effects of treatment were reported.⁴² Little is known about the components of this drug and data from larger numbers of subjects are required to allow fuller evaluation of the preparation.

The conclusions that can be made about prophylaxis are limited. However, with a rate of symptomatic thrombosis of around 0.5% for all flyers after prolonged travel it is clear that most travellers are not at high risk of developing this complication. VTE is a multicausal disorder and those at greatest risk of developing travel related thrombosis are those with a pre-existing prothrombotic state which may be congenital or acquired. Prophylactic measures are not completely without risk

and indiscriminate use is not recommended. Prophylaxis should target high risk travellers and, based on the available evidence in these individuals heparin on the day of travel should be considered.

Research directions

- Reporting of large studies into the effects of hypobaric hypoxia on coagulation activation, fibrinolytic activity and endothelial function.
- Further large studies documenting the development of clinical VTE in the 2 weeks following long distance travel, combined or followed by studies of the effect of prophylaxis.
- Prospective studies of prolonged rail and car or bus travel to confirm or refute their association with development of symptomatic VTE.

Practice points

- Most available data confirm an association between air travel and thromboembolism. Paucity of studies precludes similar conclusions on other modes of travel but given the likely importance of stasis an association is highly plausible.
- The risk of symptomatic VTE after prolonged travel of more than 8 h is around 0.5%.
- Individuals without a pre-existing risk of thrombosis are at extremely low risk of VTE.
- It is unclear whether business class travel carries a lower thrombosis risk than economy class travel.
- The risk of severe pulmonary embolism soon after flying is clearly associated with the duration of travel. For flights of greater than 12 h the risk is around 5 per million. For flights less than 6 h the risk is negligible.

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