

Air travel and venous thromboembolism

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Abstract There has recently been increased publicity on the risk of venous thrombosis after long-haul flights. This paper reviews the evidence base related to the association between air travel and venous thromboembolism. The evidence consists only of case reports, clinical case-control studies and observational studies involving the use of intermediate end-points, or expert opinion. Some studies have suggested that there is no clear association, whereas others have indicated a strong relationship. On the whole it appears that there is probably a link between air travel and venous thrombosis. However, the link is likely to be weak, mainly affecting passengers with additional risk factors for venous thromboembolism. The available evidence is not adequate to allow quantification of the risk. There are insufficient scientific data on which to base specific recommendations for prevention, other than that leg exercise should be taken during travel. Further studies are urgently needed in order to identify prospectively the incidence of the condition and those at risk.

Keywords Aircraft; Travel; Venous thrombosis/etiology; Thromboembolism/etiology; Causality; Risk factors; Epidemiologic studies (*source: MeSH, NLM*).

Mots clés Navigation aérienne; Voyage; Thrombose veineuse/étiologie; Thrombo-embolie/étiologie; Causalité; Facteur risque; Etude analytique (Epidémiologie) (*source: MeSH, INSERM*).

Palabras clave Aeronaves; Viaje; Trombosis venosa/etiología; Tromboembolismo/etiología; Causalidad; Factores de riesgo; Estudios epidemiológicos (*fuentes: DeCS, BIREME*).

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Voir page 405 le résumé en français. En la página 405 figura un resumen en español.

Introduction

The possibility of an association between air travel and potentially life-threatening venous thromboembolism has recently received increasing attention. The types of venous thromboembolic disease reported to be associated with air travel include deep vein thrombosis in calf veins (1-3), subclavian vein thrombosis (4), cerebral vein thrombosis (5), and pulmonary embolism (3, 6, 7). The causal relationship between air travel and subclavian vein thrombosis or cerebral vein thrombosis is substantially weaker than that with leg vein thrombosis. Pulmonary embolism has been reported in about one-fifth of published studies on travel-related deep vein thrombosis (8) and appears to be an important cause of sudden death among long-distance passengers (9).

Homans reported the first two cases of venous thromboembolism associated with air travel in 1954 (1) and since then a substantial number of cases have been recorded. Most of the early reports involved single cases or small series of patients (1, 2, 10). More recently, Sarvesvaran (9) reviewed sudden natural deaths that occurred over a three-year period either at London's Heathrow Airport or during flights that terminated there. Of the sudden deaths among long-distance passengers, 18% were caused by pulmonary embolism, making this the second most frequent cause of such mortality among

long-haul passengers. In a similar study, 70 cases of pulmonary embolism were reported in the medical department of the Paris airports between 1984 and 1998 (11). Some other studies are worthy of comment because of the larger numbers of people involved. Deep vein thrombosis and pulmonary embolism occurred in 44 patients in Honolulu (8), in 40 over a period of six years in Martinique (12), and in five in Germany (13). In another study in Honolulu, 33 patients were reported with venous thromboembolism after long-distance air travel (14).

There appears to be widespread agreement that prolonged immobility in a sitting position is a risk factor for venous thromboembolism. As well as air travel, other forms of long-duration travel have been suspected of precipitating venous thrombosis (15, 16). These reports highlight the important question as to whether travel is associated with venous thromboembolism but they do not provide a concrete answer.

Case-control studies

An epidemiological case-control study of deep vein thrombosis aimed at identifying risk factors for venous thromboembolism identified long-distance travel as one of the risk factors (16). Recently, two prospective case-control studies have considered this issue (17, 18). A prospective controlled study conducted in a hospital situated close to a busy airport in France found that a

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history of recent travel was almost four times more frequent in the venous thromboembolism group than in the controls (17). The odds ratio for developing venous thromboembolism among patients who travelled was 3.98 (95% confidence interval (CI) = 1.9–8.4), with the mode of transport including train or car in 30 cases and aeroplane in nine.

In another case–control study (18), the travel history of 788 patients with venous thrombosis was compared with that of controls who had similar symptoms but did not exhibit this condition. Four of the patients with deep vein thrombosis and 13 of those without the condition had travelled by aeroplane, giving an odds ratio of 1.0 (95% CI = 0.3–3.0). These results showed that for most patients who presented at hospital with deep vein thrombosis the cause was not related to air travel. In this study the frequency of travel in both patients and controls was low (5% and 7%, respectively). No information was given on the number of long-haul passengers in each group. Furthermore, the control group consisted of subjects suspected of but not confirmed as having deep vein thrombosis. Subjects who had travelled and had clots that may have spontaneously lysed would therefore have been assigned to the control group, thereby confounding the results.

To date no large-scale prospective study has examined asymptomatic travellers for the development of venous thromboembolism.

Extent of the problem

The annual incidence of deep venous thrombosis is estimated to be 1 per 1000 (19). Since there are approximately 1.4 billion passengers who fly every year, venous thromboembolism in air travellers is a very rare event (20). However, it should be noted that the published data are derived from patients who present with symptoms at medical institutions. Evidence from postmortem studies indicates that a substantial proportion of cases of venous thromboembolism are asymptomatic (21). Thus it is likely that there are two further categories of cases: passengers who are asymptomatic and those who are symptomatic but do not present at hospital.

There are few data on the incidence of venous thromboembolism related to air travel. In one study, carried out in the north of England, every person with venous thromboembolism treated over a 12-month period in five hospitals serving a relatively fixed population of 650 000 was asked about their travel history during the four weeks preceding diagnosis. A total of 26 of the 634 cases of venous thromboembolism had travelled by air over this period, giving an annual incidence of 0.4 per 10 000 (22).

Is there a real link between air travel and venous thromboembolism?

Opinion on this matter ranges from a disinclination to accept that there is such a link to the view that a causal relationship does exist.

Reviewing the published work in 1992, Milne was unable to conclude that air travel was epidemiologically associated with venous thromboembolism (23). On the basis of a review of more recent work, Forbes & Johnston concluded that, for certain individuals, long air journeys in cramped conditions do carry a risk of venous thromboembolism (20). The most

recent review of the subject suggested a strong link between travel and venous thrombosis (22).

There are a few published cases of venous thromboembolism among aircrew (4, 24, 25), who are presumably younger and fitter than the average passenger. Cabin crews are physically active during most stages in flights, and cockpit crews have adjustable seats and are not subjected to cramped seating conditions.

It can be concluded that there is a lack of hard experimental data to support the link between air travel and venous thromboembolism. A properly conducted prospective clinical trial is needed in order to investigate passengers' prothrombotic markers and the status of their calf veins before and after air travel. Such a study would have to involve a large sample so that the scale of any relationship between air travel and venous thromboembolism could be established.

Presentation of venous thromboembolism related to air travel

Deep vein thrombosis may not cause symptoms until a blockage severely interrupts the blood flow. Cramps, pain and swelling of the leg, and tenderness of the calf may then be experienced. The leg thrombosis may be asymptomatic, and the first symptoms experienced may be chest pain, shortness of breath, or palpitations as a result of venous thrombosis progressing to pulmonary embolism (26). The symptoms reported in five patients with subclavian venous thrombosis were swelling of the arm and axillary tenderness, with onset occurring during flight or immediately after arrival at a destination (4).

Symptoms of venous thromboembolism may develop within 24 hours after takeoff (8, 27). In the series reported from Honolulu (14), symptoms of venous thromboembolism started during flights in four cases, on day 1 after flights in eight cases, and before day 15 after flights in 27 cases. The median time of onset was on day 4 after flights.

Predisposing factors for venous thromboembolism related to air travel

Several studies have reviewed possible risk factors for venous thromboembolism related to air travel (20, 22, 27, 28). Possible cabin-related risk factors include immobilization, cramped sitting position, low air pressure, relative hypoxia, low humidity, and dehydration. Passenger-related factors that have been implicated include the following: overweight, chronic heart disease, other chronic diseases, hormone therapy, malignancy, previous deep vein thrombosis, recent surgery or injury of the popliteal vein wall, age over 40 years, pregnancy, and hereditary hypercoagulability. However, experimental evidence has only been reported in support of dehydration (29) and relative hypoxia (30) as risk factors.

What mechanisms might underlie the risks associated with long-haul flights?

The classic triad of an endothelial lesion, venous stasis, and hypercoagulability (31) are still considered to be important prerequisites for venous thrombosis. Venous flow velocity is two-thirds lower in a person who is sitting than in one who is supine (32, 33). After an hour of quiet sitting, a progressive rise

in haematocrit and a concomitant increase in plasma protein concentration have been reported (34). Simons & Krol (35) showed that healthy persons exposed to an eight-hour simulated flight at an altitude of 8000 feet (2438.4 m) and at a relative humidity of 8–10% exhibited increased mean plasma osmolality, mean urine osmolality, and urine specific gravity, indicating dehydration. Decreased air pressure and relative hypoxia in an aeroplane cabin may reduce fibrinolytic activity in endothelial cells (30). A cramped position could also cause venous stasis by external compression from the seat and by “kinking” the popliteal veins, especially among elderly persons. It thus seems likely that during a flight many complex rheological and biochemical alterations could occur in seated persons that could precipitate the formation of a venous thrombus.

Outcome of a WHO consultation on air travel and venous thrombosis

In March 2001, WHO convened an international meeting on air travel and venous thrombosis at which experts on venous thromboembolism and representatives of airline companies, the International Air Transport Association (IATA), the International Civil Aviation Organization (ICAO), the European Commission and consumer groups participated (36). The objectives were to review the scientific information on air travel and venous thromboembolism, identify gaps in knowledge, and develop priority areas for research.

It was concluded that a link probably exists between air travel and venous thrombosis and that similar associations possibly exist for other forms of travel. Participants agreed

that the risk was not quantifiable because of a lack of data, and that it was likely to be small and mainly affect passengers with additional risk factors for venous thromboembolism. Also it was concluded that there were insufficient scientific data on which to make specific recommendations for prevention, except that leg exercise should be taken during travel. The indiscriminate use of pharmacological agents was discouraged because of their recognized side-effects. The following priorities for research were identified.

- A set of multicentre international epidemiological studies, including a large prospective cohort study examining hard clinical end-points, should be conducted in order to determine whether there was a link between air travel and venous thrombosis; the absolute risk if such a link exists; and the size of the problem. These studies would also provide clues to other etiological factors.
- Special studies should be conducted in order to seek intermediate end-points in groups of volunteers and examine isolated independent environmental and behavioural risk factors.
- An intervention study involving passengers prospectively, using objective diagnostic methods and examining various modes of intervention, should be carried out.

It was agreed that these studies should be undertaken as soon as possible under the auspices of WHO and ICAO, supported by an independent scientific committee, in collaboration with IATA and airline companies. ■

Conflicts of interest: none declared.

Résumé

Voyages aériens et thrombo-embolie veineuse

Une importante publicité a récemment été faite autour du risque de survenue d'une thrombose veineuse après un voyage aérien de longue durée. Le présent article examine les données concernant l'association entre les voyages aériens et la thrombo-embolie veineuse. Il s'agit uniquement de comptes rendus de cas, d'études cas-témoins et d'études d'observation utilisant des critères intermédiaires, ou encore d'avis d'experts. Certaines études tendaient à montrer qu'il n'existait pas d'association claire, tandis que d'autres indiquaient l'existence d'une relation marquée. Dans l'ensemble, il apparaît qu'il existe probablement un lien entre les

voyages aériens et la thrombose veineuse, mais ce lien est vraisemblablement faible et concerne surtout les passagers qui présentent d'autres facteurs de risque de thrombo-embolie veineuse. Les données disponibles ne permettent pas de quantifier le risque. Il n'existe pas suffisamment de données scientifiques pour que l'on puisse établir des recommandations spécifiques en vue de la prévention, autres que des exercices des membres inférieurs à pratiquer pendant le vol. Il est urgent et nécessaire de réaliser des études plus poussées afin de déterminer de façon prospective l'incidence de cette affection et de définir les sujets à risque.

Resumen

Viajes aéreos y tromboembolismo venoso

Últimamente se ha hablado mucho de los riesgos de trombosis venosa asociados a los vuelos de larga duración. En este artículo se analiza la evidencia disponible sobre la relación existente entre el uso del avión y el tromboembolismo venoso. Esa evidencia se basa sólo en informes de casos, estudios clínicos de casos y controles y estudios observacionales en los que se han utilizado criterios de evaluación intermedios o la opinión de expertos. Algunos estudios parecen indicar que no existe una relación clara, mientras que otros revelan una relación muy marcada. Globalmente parece probable la existencia de una relación entre

los viajes aéreos y la trombosis venosa. Ahora bien, esa asociación es posiblemente débil, y afectaría principalmente a los pasajeros con factores de riesgos adicionales para sufrir tromboembolismo venoso. La evidencia disponible no permite cuantificar el riesgo. No hay datos científicos suficientes para poder formular recomendaciones específicas con miras a la prevención, aparte del consejo de mover las piernas durante el viaje. Es necesario hacer urgentemente nuevos estudios para identificar prospectivamente la incidencia de la enfermedad y las personas en riesgo.

References

- Homans J. Thrombosis of the leg veins due to prolonged sitting. *New England Journal of Medicine* 1954;250:148-9.
- Marshall M. Air travel thrombosis. *Münchener Medizinische Wochenschrift* 1982;124(17):83.
- Arfvidsson B, Eklof B, Kistner RL, Masuda EM, Sato DT. Risk factors for venous thromboembolism following prolonged air travel. *Hematology/Oncology Clinics of North America* 2000;14:391-400.
- Cable GG. Hyperhomocysteinaemia and upper extremity deep venous thrombosis. A case report. *Aviation Space and Environmental Medicine* 1999;70:701-4.
- Pfausler B, Vollert H, Boesch S, Schmutzhard E. Cerebral venous thrombosis — a new diagnosis in travel medicine? *Journal of Travel Medicine* 1996;3:165-7.
- McDonald RC. Pulmonary embolism associated with air travel. *New England Journal of Medicine* 2002;346:138-9.
- Symington IS, Stack BHR. Pulmonary thromboembolism after travel. *British Journal of Diseases of the Chest* 1977;71:138-40.
- Eklof B, Kistner RL, Masuda EM, Sonntag BV, Wong HP. Venous thromboembolism in association with prolonged air travel *Dermatologic Surgery* 1996;22:637-41.
- Sarvesvaran R. Sudden natural deaths associated with commercial air travel. *Medicine, Science and Law* 1986;1:35-8.
- Thomas JEP, Abson CP, Cairns NJW. Pulmonary embolism. A hazard of air travel. *Central African Journal of Medicine* 1981;27(5):85-7.
- Clerel M, Caillard G. [Thromboembolic syndrome due to prolonged sitting position and long-haul flights: the experience of the Aeroports de Paris emergency medical service.] *Bulletin de l'Académie Nationale de Médecine* 1999;183(5):985-97 (in French).
- Ribier G, Zizka V, Cysique J, Donatien Y, Glaudon G, Ramialison C. [Venous thromboembolic incidents after air travel. A retrospective study of 40 cases recorded in Martinique.] *Revue de Médecine Interne* 1997;18:601-4 (in French).
- Nissen P. The so-called economy class syndrome or travellers' thrombosis. *Journal of Vascular Disease* 1997;26:239-46.
- Mercer A, Brown JD. Venous thromboembolism associated with air travel: a report of 33 patients. *Aviation Space and Environmental Medicine* 1998;69:154-7.
- Tardy B, Page Y, Zeni F, Decousus H, Comtet C, Cusey I, et al. Phlebitis following travel. *La Presse Médicale* 1993;22(17):811-4.
- Samama M. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients. *Archives of Internal Medicine* 2000;160:3415-20.
- Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease. A case-control study. *Chest* 1999;115:440-4.
- Kraaijenhagen RA, Haverkamp D, Koopman MM, Pransoni P, Piovella F, Buller HR. Travel and risk of venous thrombosis. *Lancet* 2000;356:1492-3.
- Rosendaal FR. Venous thrombosis, a multicausal disease. *Lancet* 1999;353:1167-73.
- Forbes CD, Johnston RV. Venous and arterial thrombosis in airline passengers. *Journal of the Royal Society of Medicine* 1998;91:565-6.
- Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *Journal of the Royal Society of Medicine* 1989;82(4):203-5.
- Kesteven PLJ. Travellers' thrombosis. *Thorax* 2000;55(Suppl 1):S32-6.
- Milne R. Venous thromboembolism and travel: is there an association? *Journal of the Royal College of Physicians of London* 1992;26:47-9.
- Steinhauser RP, Stewart JC. Deep venous thrombosis in the military pilot. *Clinical Medicine* 1989;60:1096-8.
- Emonson DL. Activated protein C resistance as a new cause of deep venous thrombosis in aviators. *Aviation Space and Environmental Medicine* 1997;68:606-8.
- Black J. Deep-vein thrombosis and pulmonary embolism. *Lancet* 1993;342:352-3.
- Arfvidsson B. Risk factors for venous thromboembolism following prolonged air travel: a "prospective" study. *Cardiovascular Surgery* 2001;2:158-9.
- Giangrande PLF. Thrombosis and air travel. *Journal of Travel Medicine* 2000;7:149-54.
- Carruthers M, Arguelles AE, Mosovich A. Man in transit: biochemical and physiological changes during intercontinental flights. *Lancet* 1976;8:977-80.
- Bendz B, Rostrop M, Sevre K, Andersen TO, Sandset PM. Association between acute hyperbaric hypoxia and activation of coagulation in human beings. *Lancet* 2000;356:1657-8.
- Virchow R. [*Collected works on scientific medicine.*] Frankfurt: Meidinger; 1856 (in German).
- Henriksen O. Local nervous mechanism in regulation of blood flow in human subcutaneous tissue. *Acta Physiologica Scandinavica* 1976;97:385-91.
- Wright HP, Osborn SB. Effects of posture on venous velocity, measured with ²⁴NaCl. *British Heart Journal* 1952;14:325-30.
- Moyses C. Economy class syndrome. *Lancet* 1988;2:1077.
- Simons R, Krol J. Jet lag, pulmonary embolism and hypoxia. *Lancet* 1996;348:416.
- Report of the Consultation on Air Travel and Venous Thromboembolism.* Geneva: World Health Organization; 2001. Unpublished document WHO/CVD/venous thromboembolismD/2001.3.