Travelers' Thrombosis

Raymond V. Johnston and Martin F. Hudson on behalf of the Aerospace Medical Association Air Transport Medicine Committee*

Johnston RV, Hudson MF, on behalf of the Aerospace Medical Association Air Transport Medicine Committee. *Travelers' thrombosis*. Aviat Space Environ Med 2014; 85:191–4.

The suggestion that venous thromboembolism (VTE) is associated with air travel has for several decades been the subject of both "media hype" and extensive debate in the medical literature. As emotion and anecdote is often a feature in this debate, it is therefore necessary to separate evidence from anecdote. "Travelers' thrombosis" is a more appropriate term because the evidence suggests that any form of travel involving immobility lasting more than 4 h can predispose to thrombosis. There is no unique factor in the air travel cabin environment that has been shown to have any effect on the coagulation cascade. Prevention of thrombosis in any form of travel, including air travel, requires being aware of the issue and making an adequate risk assessment together with appropriate prophylactic measures.

Keywords: travelers' thrombosis, air travel, evidence, immobility, passenger heath, risk assessment, prophylaxis.

VENOUS THROMBOEMBOLISM is not a new disease. It was Virchow (30) who classically described that deep venous thrombosis (DVT) can be associated with a triad of factors: changes in blood flow, alterations in blood viscosity, and abnormalities in the wall of the blood vessel. As long ago as 1940, Simpson (27), the eminent pathologist, studied patients who had rested in deck chairs in the underground during the blitz of London and showed there was an increased risk for the development of venous thromboembolism (VTE). It should be remembered that these deck chairs were quite primitive in the 1940s and that the lower part of the seat had a rigid transverse bar which caused considerable pressure on the back of the thigh. When the deck chairs were replaced by bunks, the prevalence of VTE decreased markedly. The bunks obviated this problem as the user was lying in a recumbent posture. Similarly, Homans (13) in 1954 described five patients, two associated with air travel, two with car journeys, and one while sitting in the theater, who developed venous thromboembolism. In Europe the annual incidence of VTE has been estimated by Nordstrom et al. (22) and Hansson et al. (10) to be between 1.6 and 1.8 per 1000. Oger (24), in a community-based study in France, confirmed these figures and also showed that the incidence rose markedly with age, with those over the age of 75 having an incidence of 1 per 100 of the population.

Travelers' Thrombosis

Symington and Stack (28) described eight cases of VTE following travel. Three had traveled by car, three by aircraft, one by rail, and one by rail and ship travel combined. Just as Homans (13) had reported, they found the condition was not unique to air travel. In 1988, Cruickshank (7) coined the unfortunate phrase, "economy class syndrome" when he described six case reports of VTE. As is now quite clear, this term is a misnomer and it is unfortunate and unhelpful that it is still found in some media reports on the subject. The Aerospace Medical Association's Air Transport Medicine Committee (2) stated that the phrase "economy class syndrome" is seriously misleading and the term "travelers' thrombosis" should be used. This view was also supported by the UK House of Lords Select Committee on Science and Technology (14).

The evidence for the association of travel and VTE has been studied in a number of publications. Kraaijenhagen (18) studied 788 patients with a diagnosis of possible deep venous thrombosis. The data in this paper showed that the odds ratio for air travel was 1.0 (95% CI: 0.3–3.0). This is the only publication which failed to show any association.

In a case control study of 160 individuals, Ferrari (8) found a history of air travel in those who presented with VTE in 24.5% of cases as against 7.5% in those who did not present with VTE ($P < 0.0001$). The odds ratio for venous thromboembolism was 3.98 (95% CI: 1.9–8.4). In this study 28 individuals had traveled by car, 9 by air, and 2 by train and the duration of travel was 5.4 ± 2.1 h.

*A report prepared by the Air Transport Medicine Committee. Members of the committee are: Martin F. Hudson (Chair), Alex M. Wolbrink (Co-Chair), Nomy Ahmed, Soha S. Albayat, Paulo M. Alves, Michael Bagshaw, Nadia Qassim Bastaki, Jorge O. Behaine, Yehezkel G. Caine, Chun Hon Chong, Robert A. Cocks, Nigel P. Dowdall, Anthony D. Evans, Sally A. Evans, Silvio Finkelstein, Kevin C. Herbert, Stephen J. Houston, Liliana Jimenez, Kevin C. Herbert, Stephen J. Houston, Liliana Jimenez, Raymond V. Johnston, Steffen Luduch, Simon May, Stuart J. Mitchell, Ian A. Mollan, Pooshan D. Navathe, Hugh J. O'Neill, Rose M. Ong, Robert R. Orford, Frank S. Pettyjohn, Rui M. C. Pombai, David M. C. Powell, Fiona M. Rennie, Philip J. Scarpa Jr., Jarnail Singh, Surendra Sodhi, Timothy Sprott, Tim Stevenson, Claude Thibeault, Roland L. M. A. Vermeiren, Elizabeth S. Wilkinson, and Hui Kian Chris Yeo.

This manuscript was received for review in July 2013. It was accepted for publication in October 2013. It was subjected to full peer review by *Aviation, Space, and Environmental Medicine.*

Address correspondence and reprint requests to: Aerospace Medical Association, 320 S. Henry St., Alexandria, VA 22314.

DOI: 10.3357/ASEM.3822.2014

Despite this convincing evidence that VTE can occur in any form of transport when associated with prolonged immobility, it has still been suggested that the coagulation cascade may be activated by the aircraft cabin environment and enhance the risk in this particular mode of transport. Bendz (4) showed that in volunteers who were exposed to hypobaric hypoxia, a transient activation of coagulation up to eightfold occurred. However, in this study there was no control group and this finding, therefore, needs to be treated with a degree of suspicion, as measurements were made in the same individual before and after exposure to hypobaric hypoxia. This situation was later clarified by Toff et al. (29), who showed that there was no activation of coagulation in a controlled decompression chamber study simulating the standard cabin environment. In this study a single blind cross-over technique was used.

Scurr (25) raised further doubts, suggesting that in those passengers flying for more than 8 h, there was a 10% prevalence of what was described as "thrombosis." However, this "diagnosis" was merely a positive ultrasound scan, with a negative D-dimer (a sensitive indicator of fibrinolysis associated with DVT). As the scan was not confirmed using a 'gold standard' technique and the numbers in the study were small, the statistical significance of these findings is in doubt. However, it is interesting to note that of those passengers who wore compression stockings, none had a positive scan. The "10% prevalence" is considerably higher than the figures from the general population referred to earlier in this paper, so these results are surprising. However, Hirsh and O'Donnell (1), in a commentary in the same issue of the *Lancet*, criticized the validity of the data in this study and others. NHS MeReC Bulletin (21) and Bagshaw (3) have also received the data with some skepticism.

Lapostolle et al. (20) was one of the earliest reports which showed that the incidence of VTE increases with the distance traveled. This was a retrospective study that examined passengers arriving at Charles de Gaulle Airport between 1993 and 2000. There were 135.29 million passengers and 56 cases of VTE. In those who had traveled less than 5000 km, the prevalence of VTE was 0.01 per million. This incidence rose to 4.8 per million in those who had traveled greater than 10,000 km. As distance traveled is a surrogate for the duration of travel, this clearly shows that increasing journey length increases the prevalence of the disease. However, the numbers of cases of VTE is considerably smaller than the 10% figure postulated by Scurr (26).

It has been suggested that as pilots and cabin crew have more exposure to the aviation flight environment than the majority of passengers, that if there was any exposure in the aviation environment which predisposes to thrombosis, then they would be more prone to VTE. However, as cabin crew are much more mobile than pilots in the flying environment, this fact would reduce the risk of DVT occurring in this particular occupational health group. In fact, the proportional mortality ratio of 93 for pulmonary embolism in flight crew is lower than the normal population (23). In 2001 the UK Civil Aviation Authority performed a study which showed that the incidence of VTE in the pilot community was 0.2 per thousand per year, which is considerably less than the general population. Even allowing for the healthy worker effect, there is no evidence from these data that suggest there is any activation of coagulation in this occupational group (17).

Robust data on the incidence of VTE and travel has been published by The World Health Organization Research into the Global Hazards of Travel (WRIGHT Project) (31). The first report from this research was in 2006 by Cannegieter et al. in the Multiple Environmental and Genetic Assessment (MEGA) Study (5), which showed that the risk of venous thrombosis was moderately increased for all modes of travel whether by air, car, bus, or train. This study listed the following well-recognized risk factors for the development of VTE:

- Immobility
- Recent surgery
- Recent trauma
- Abnormalities of blood clotting
- Previous or family history of DVT
- Malignancy
- Pregnancy
- Estrogen: OC or HRT
- Increasing age over 40 years
- Chronic heart disease
- Obesity
- Chronic venous insufficiency

The study also confirmed that these risk factors, such as excessive body weight, blood clotting abnormalities, and oral contraceptives, are significant factors in the general population and are not particularly associated with the aviation environment.

The final report from the WRIGHT Project phase one study, performed in a cohort of healthy individuals, showed that the absolute risk of VTE in flights greater than 4 h was 1 in 6000. Kuipers (19), in a separate publication in a cohort study of 8755 traveling employees, found that the exposed incident rate ratio was 3.2 (1.8–5.6) and that the absolute risk of DVT was 1 in 4656 flights. Higher rates were also seen in specific risk groups, e.g., oral contraceptive use and those who were overweight or extremely tall.

Prophylaxis

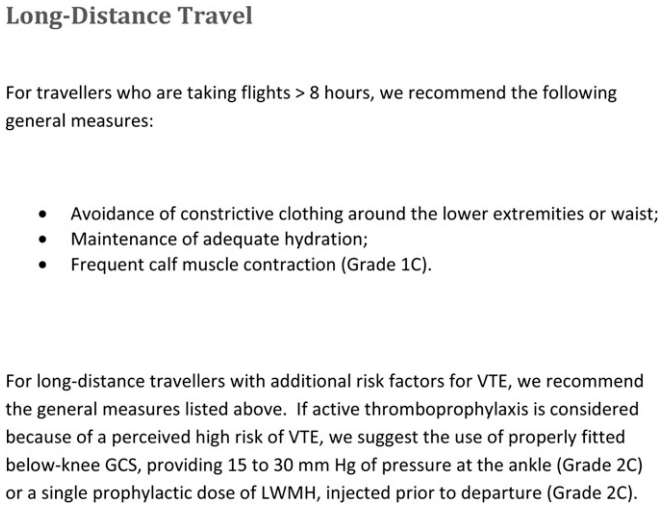
The evidence for a moderate increase (three to four times) in thrombosis associated with travel on flights of 4 h or greater (9) poses the question of what preventative strategy should be adopted to minimize the risk. Upgrading to a business class seat, which could be the intuitive approach, is not supported by evidence. The BEST Study (16) showed that there was no difference between the incidence of VTE between business and economy class.

What is required is an individual risk assessment to ascertain whether a specific predisposition to thrombosis exists. As previously described and further confirmed in the LONFLIT Study (9), in 75% of passengers traveling by air immobilization is a significant factor. It is therefore most important to encourage mobility,

particularly in those who already have other risk factors. If the risk is perceived to be particularly high, then the use of properly fitted antiembolism stockings or formal anticoagulation with low molecular weight heparin (LMWH) or warfarin needs to be considered. The benefit of using prophylactic anticoagulation treatment was studied by Cesarone et al. (6), who studied three groups using high-dose Enoxaparin (1 mg · kg^{-1}) 2–4 h prior to travel lasting between 7 and 8 h and compared this with aspirin one dose daily for 3 d starting 12 h before travel vs. control. The results of this study showed that there were 0 of 82, 3 of 84, and 4 of 83 asymptomatic DVT in the 3 groups, respectively. No symptomatic DVT or pulmonary embolism events occurred in any of the groups. However, this study had only a very small sample size and, as follow-up ended after the individuals left the airport, the significance of these findings is limited. Also, aspirin has not been shown in any scientific study to have any significant beneficial effect on the venous side of the circulation. The American College of Chest Physicians evidence-based practice guidelines (12) for the prophylaxis of VTE are shown in **Fig. 1** together with the grades of evidence for their use. This subject was reviewed by the UK House of Lords Science and Technology Committee in 2007 (15).

Whenever a robust risk assessment is necessary in airline passengers, particularly those at high risk, both the passenger and their advising physician should be fully cognizant of the issues involved. In order to enhance the comfort and pleasure of air travel, several airlines (29) now produce in-flight magazines and safety videos on their websites, with good health information on several aspects of air travel, and this includes travelers' thrombosis. In some countries such as the UK organizations like the Aviation Health Unit of the UK CAA (1) also make information available. However, a recent study by Scurr (26) reviewing the websites of approximately 100 airlines found that only about 25% were warning of the risks of travelers' thrombosis, so there is room for considerable improvement. The Aerospace Medical Association's Air Transport Medicine Committee encourages any initiatives which enhance awareness and better understanding of this potential health issue in travelers. This paper is a contribution to that debate and the committee is committed to encouraging all airlines to consider their own position on this important subject and to comply with the recommendations made in this paper.

In conclusion, there is an increased risk of thrombosis with prolonged travel by train, bus, plane, or car. The approximate three to fourfold increase in relative risk requires attention with respect to provision of advice to travelers. Targeting individuals with increased risk and applying appropriate prophylaxis means the majority of individuals may fly without any undue risk.



Long-Distance Travel

For travellers who are taking flights > 8 hours, we recommend the following general measures:

- Avoidance of constrictive clothing around the lower extremities or waist;
- Maintenance of adequate hydration;
- Frequent calf muscle contraction (Grade 1C).

For long-distance travellers with additional risk factors for VTE, we recommend the general measures listed above. If active thromboprophylaxis is considered because of a perceived high risk of VTE, we suggest the use of properly fitted below-knee GCS, providing 15 to 30 mm Hg of pressure at the ankle (Grade 2C) or a single prophylactic dose of LWMH, injected prior to departure (Grade 2C).

For long-distance travellers, we recommend against the use of aspirin for VTE prevention (Grade 1B).

Fig. 1. Recommendations for DVT prevention (12).

REFERENCES

1. Aviation Health Unit UK. Gatwick Airport South, West Sussex, UK: CAA; no date. Retrieved July 2013 from http://www.caa.co.uk/default.aspx?catid=923.
2. Bagshaw M. Traveller's thrombosis: a review of deep vein thrombosis associated with travel. Air Transport Medicine Committee, Aerospace Medical Association. Aviat Space Environ Med 2001; 72:848–51.
3. Bagshaw M. A response to "The effect of high altitude commercial air travel on oxygen saturation. Anaesthesia 2005; 60:948.
4. Bendz B, Rostrup M, Sevre K, Andersen TO, Sandset PM. Association between acute hypobaric hypoxia and activation of coagulation in human beings. Lancet 2000; 356:1657–8.
5. Cannegieter SC, Doggen CJ, van Houwelingen HC, Rosendaal FR. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). PLoS Med 2006; 3:e307.
6. Cesarone MR, Belcaro G, Nicolaides AN, Incandela L, De S, et al. Venous thrombosis from air travel: the LONFLIT 3 study—prevention with aspirin vs. low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. Angiology 2002; 53:1–6.
7. Cruickshank JM, Gorlin R, Jennett B. Air travel and thrombotic episodes: the economy class syndrome. Lancet 1988; 332:497–8.
8. 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.
9. Geroulakos G. The risk of venous thromboembolism from air travel. BMJ 2001; 322:188.
10. Hansson PO, Welin L, Tibblen G, Eriksson H. Deep vein thrombosis and pulmonary embolism in the general population. Arch Intern Med 1997; 157:1665–70.
11. Hirsh J, O'Donnell MJ. Venous thromboembolism after long flights: are airlines to blame? Lancet 2001; 357:1461–2.
12. Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. American College of Chest Physicians. Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6, Suppl.): 71S–109S.
13. Homans J. Thrombosis of the deep leg veins due to prolonged sitting. N Engl J Med 1954; 250:148–9.
14. House of Lords Select Committee on Science and Technology. Air travel and health. Session 1999-2000, 5th Report, HL Paper 121-I. London: The Stationery Office; 2000.
15. House of Lords Select Committee on Science and Technology. Air travel and health. Session 2007-2008, 1st Report, HL Paper 4.15 -4.17. London: The Stationery Office; 2008.
16. Jacobson BF, Munster M, Smith A, Burnand KG, Carter A, et al. The BEST Study – a prospective study to compare business class versus economy class air travel as a cause of thrombosis. S Afr Med J 2003; 93:522–8.
17. Johnston R, Evans A. Venous thromboembolic disease in pilots. Lancet 2001; 358:1734.

18. Kraaijenhagen RA, Haverkamp D, Koopman MM, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. Lancet 2000; 356:1492–3.
19. Kuipers S, Cannegieter SC, Middeldorp S, Robyn L, Büller HR, Rosendaal FR. The absolute risk of venous thrombosis after air travel: a cohort study of 8,755 employees of international organisations. PLoS Med 2007; 4:e290.
20. Lapostolle F, Surget V, Borron SW, Desmaiziéres M, Sordelet D, et al. Severe pulmonary embolism associated with air travel. N Engl J Med 2001; 345:779–83.
21. NHS MeReC Bulletin. Venous thromboembolism. MeReC Bulletin 2003; 13(4):13–16.
22. Nordström M, Lindblad B, Bergqvist D, Kjellström T. A prospective study of the incidence of deep vein thrombosis within a defined urban population. J Intern Med 1992; 232:155–60.
23. Office of Population and Census Statistics. Occupational health decennial supplement. London: HMS Stationary Office; 1995. OPCS Series DS No. 10.
24. Oger E. Incidence of venous thromboembolism: a community based study in Western France. EPI-GETBP Study Group. Thromb Haemost 2000; 83:657–60.
25. Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. Lancet 2001; 357:1485–9.
26. Scurr JR, Ahmad N, Thavarajan D, Fisher RK. Travellers' thrombosis: airlines are still not giving passengers the WRIGHT advice. Phlebology 2010; 25:257–60.
27. Simpson K. Shelter deaths from pulmonary embolism. Lancet 1940; 236:744.
28. Symington IS, Stack BHR. Pulmonary thromboembolism after travel. Br J Dis Chest 1977; 71:138–40.
29. Toff WD, Jones CI, Ford I, Pearse RJ, Watson HG, et al. Effect of hypobaric hypoxia, simulating conditions during long-haul air travel, on coagulation, fibrinolysis, platelet function, and endothelial activation. JAMA 2006; 295:2251–61.
30. Virchow R. Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt: Meidinger; 1856.
31. WHO. WHO Research into Global Hazards of Travel (WRIGHT) project: final report of phase 1. Geneva: World Health Organization; 2007.