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TRAVEL AS A RISK FACTOR FOR VENOUS THROMBOEMBOLIC DISEASE

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Abstract: There is increasing evidence that prolonged travel may be associated with the development of venous thromboembolic disease: ie deep venous thrombosis and pulmonary embolism. The data from case reports, retrospective reviews and case control studies have been confirmed by prospective studies.

There have been several prospective studies of subjects embarking on airline flights of greater than 4 hours duration aimed at determining the incidence of DVT as detected by ultrasonography. In unprotected subjects, the incidence of thrombosis in the calf veins or muscular veins ranged between 0% and 10%.

There is evidence that the incidence of travel-related pulmonary embolism appears to be related to the distance travelled and immobility during the flights. Whether the imputed causation is merely due to immobility and venous compression or to other factors associated with the aircraft cabin requires further clarification.

The use of below-knee graduated compression stockings appears to be highly effective. A 100 AXa U/kg single dose of a low molecular weight heparin, given 2-4 hours before the flight, have been reported to be more effective than aspirin and placebo. However, the benefit/risk ratio of such a strategy remains to be assessed.

Key words: Travel; deep vein thrombosis; pulmonary embolism

INTRODUCTION

The "economy class syndrome" was made famous in 1988 by Cruikshank, who reported, in *The Lancet*, a series of pulmonary embolisms (PE) occurring after air travel in economy class [1].

Although the term had already been used by others [2] to refer to the onset of deep vein thrombosis (DVT) after long-haul flights, its main interest was the wise media exposure to which it gave rise. The term had nevertheless been used by others before him [2] to refer to the onset of deep vein thrombosis (DVT) after long flights.

Although Virchow [3], as early as 1858, described venous stasis as one of the main risk factors of DVT, a relationship between sitting and the risk of DVT was described for the first time only in 1948 by Simpson [4] This British surgeon noted a considerable increase in fatal PE rates in British soldiers forced to remain in a crouched position for several hours in shelters during the London blitz. However, it was Homans [5], in 1954, who was the first, on the basis of four cases, to suggest the probable relationship between a long journey in a sitting position and a DVT and/or PE. He suggested that "prolonged sitting as is the case in aeroplane seats, cars, etc, or even at the theatre may cause thrombosis of the veins of the lower limbs." Several series have been published since [6-8].

According to Sarvesvaran, who collected data on 61 deaths occurring during flights over a 3-year period, PE was suspected to be the cause of death in almost 20% of cases, most of these sudden deaths occurring in individuals with no past history [9].

This risk of DVT was long seen as connected only to airplane flights. However, it is likely that other situations in which people sit for several hours are also associated with a risk of venous stasis, i.e. circulatory slowing, a major feature of Virchow's triad.

This problem was considered sufficiently alarming that, in 2000, the Geneva-based World Health Organization (WHO) decided, with the collaboration of a group of "experts," to take the matter in hand. Furthermore, this problem is the topic of a chapter in the forthcoming recommendations of the American College of Chest Physicians to be published in June 2004.

CURRENT EPIDEMIOLOGICAL DATA

Using data in a register on venous thromboembolic disease [10], we undertook the first case-control study with the aim of determining whether the fact of travelling was a venous thromboembolic disease risk factor. A history of travel covered all journeys by plane, train, bus, or car lasting more than 4 hours during the month prior to diagnosis of DVT or PE. Comparison of the travel history of a group of patients suffering from confirmed DVT/PE (n = 160) with that of a matched cohort (n = 160) led to the conclusion that travelling was associated with a very significant risk of DVT/PE: OR 3.98 (95%CI: 1.9-8.4; $P < 0.001$) [11].

Since our study, several case control studies have been reported [12-14]. Although discussion is

still ongoing, these studies tend to demonstrate an association between prolonged travel and VTE. One concern, however, still remains about the exact magnitude of the problem, and the role of immobility, venous compression and other risk factors [15-23].

So far, several prospective studies have been performed and published. These studies included subjects taking plane flights of more than 4 hours duration and aimed at determining the incidence of DVT as detected by ultrasonography when no prophylaxis was used [24-28]. In particular, the first prospective study by John Scurr, a British vascular surgeon, showed that, following long flights, up to 10% of travellers, without prevention, may develop asymptomatic DVTs which can be seen by duplex ultrasonography [24]. All in all, in unprotected subjects, the incidence of thrombosis in the calf veins or muscular veins ranged between 0% and 10%. There were 19 asymptomatic DVTs among 953 "low risk" travellers (2.0%) [24-28] and 34 DVTs among 894 unprotected "high risk" travellers (3.8%) [25, 27].

The length of the journey is an important factor. The study by Lapostolle reviewing all cases seen at Roissy Airport, Paris, i.e. upon disembarkation, reported a linear relationship between the length of the flight and the risk of PE on arrival [29]. Following flights of more than 5000 km, 1.5 travellers per million may suffer PE vs 0.01 cases per million travellers on shorter flights.

Since Homans in 1954, several reported cases and a number of retrospective surveys, including our own case-control trials, have described deep vein thromboses after car, bus, or train travel [11].

Clinical Presentation and Pathophysiology

Classic clinical symptoms may occur during the trip itself, immediately after it, or up to several weeks later. In published prospective studies the majority of DVT were asymptomatic. Prevention studies in surgery have clearly shown that the vast majority of DVTs are asymptomatic. Does this mean that such asymptomatic episodes are danger-free? Bearing in mind the number of PEs due to DVTs which have not given rise to symptoms, as well as the number of cases of postphlebitic disease seen without any known earlier episode of acute DVT, it is obvious that a lot of episodes of DVT go undiagnosed. It is thus possible that long journeys, or even sitting for prolonged periods, is a largely unrecognized cause of DVT/PE, some of which may become symptomatic only long after the causal phenomenon.

Presenting symptomatology is more often that of DVT than of PE. In some cases, the first symptom may be a paradoxical embolism responsible for a stroke [30].

Currently, there appears to be no available data permitting definition of a particular topography of travel-related DVT. Sitting, together with compression of the popliteal fossa, may trigger stasis in the calves, particularly because of physiological Cockett's syndrome of the left leg. Some authors report a more frequent suprapopliteal site of clot location [23] while, in our study, the topography of the venous thrombus did not appear to follow any particular pattern [11].

Some data in the literature tend to show the existence of predisposing factors [14, 17, 21]. A correlation between the risk of venous thrombosis due to prolonged sitting and resistance to activated protein C was first suggested [31] in 1995. After a public transport strike in France lasting 3 weeks, certain carriers of Leiden V mutation who had spent long periods sitting in their cars developed a DVT while others with the mutation who had walked to work remained asymptomatic. One can assume therefore that factors predisposing to demonstrated venous thrombosis could also favor the formation of venous clots in travellers.

The pathophysiology of traveler's venous thromboembolic disease is often mentioned in the literature. Venous stasis secondary to immobility in a sitting position seems to constitute the chief suspect. We have all noticed how difficult it is sometimes to put one's shoes back on after a long car or aeroplane trip. Wright and Osborn [32], using labeled radioactive NaCl injected into the veins of the dorsum of the foot, showed that the velocity of venous flow in the lower limbs is reduced by two thirds when sitting. Stasis is often increased by compression of calf or thigh muscles against seats by sitting cross-legged. After an hour in such a position, in addition to decreased venous flow, there is a gradual increase in hematocrit and a concomitant rise in proteins of as much as 25%. Patients are often affected by profound inertia and apathy, with decreased muscle activity and thus venous return, thereby worsening the venous stasis. The problem of the formation of venous clots during flights has also been extensively discussed. It seems likely that several factors are involved.

Some authors emphasize dehydration, especially in relation to air travel. This is believed to result from the combination of drinking alcohol (diuretic effect) and a low intake of rehydrating beverages, together with the low relative humidity (8% to 12%) in high-altitude aircraft. In 1976, Carruthers et al. [33] showed decreased urine output with increased urine osmolarity during flights. Simons and Krol [34] described, in otherwise healthy individuals, increased plasma and urine osmolarity, despite a water intake of more than 2 L during

the flight in simulated, low-altitude (8000 feet) conditions lasting 8 hours. Other more recently cited possible causes are spontaneously decreased fibrinolysis and activation of coagulation associated with decreased atmospheric oxygen concentration [35, 36]. At the (very low) altitude of 8000 feet, i.e. 2400 meters, oxygen pressure is about 75 kPa. At this pressure, hemoglobin 02 saturation in healthy subjects may reach values of up to 90%, with considerable variations between individuals.

In particular, drops in O_2 saturation to values of 80% seem quite commonplace [35].

Prevention

In our opinion, prevention treatment must not do more harm than the disorder.

It would be very risky (and costly) to envisage routine preventive heparin, even at low molecular weight. Similarly, aspirin has no proven efficacy as a preventive measure.

The most effective precautions are simple, commonsense measures which cost nothing.

In order to offset the risk of dehydration, it is advisable to drink frequently, as well as to avoid alcoholic drinks. Recently there has been some concern following suspicions that tranquillizers and sleeping-pills might be involved in the pathogenesis of DVT [37].

Flexing the feet and frequent stretching of the calf muscle suffice to double or triple venous flow for several seconds. These movements should be repeated regularly several times per hour. Some airlines have installed "steppers" under each seat to enable and encourage these movements. Others show films advising such movements and warning against the risk of thrombosis.

Getting up to walk down the aisle is not always easy but is advisable when technically possible. In a car or in a train, the same preventive measures apply, the only difference being that walking (by stopping the car regularly or walking along the train corridor) is easier than in a plane.

Wearing elastic support stockings may be useful. The use of below-knee properly-fitted graduated compression stockings providing 15-30 mm Hg compression and, applied before departure, practically eliminated asymptomatic thrombosis in four randomized trials with combined samples of 1676 air travellers [24, 25, 26]. In Scurr's study, none of the patients wearing elastic stockings developed DVT, which appears to demonstrate the efficacy of this simple procedure [24]. However, the same study reported a non-negligible incidence of superficial phlebitis in these same wearers of elastic stockings. Many manufacturers have already seized the opportunity by marketing socks with potentially sufficient support properties which are easy to wear or even comfortable.

Do we need more prevention ?

In high-risk travellers (mainly those with previous history of idiopathic DVT/PE), a single, non-usual dose of LMWH, i.e. 100 AntiXa U/kg, given 2 to 4 hours before the flight, has been reported to significantly decrease the incidence of DVT when compared with placebo or even 400 mg of Aspirin started 12 hours before the flight and continued for 3 days (DVT rates = 0%, 3.6% and 4.8%, respectively) [27]. The use of LMWH in high-risk patients might be useful. However, in this study only 82 travellers received LMWH and the benefit/risk ratio will necessitate to be assessed in further studies. However, in another study (LONFLIT 4) the «control group» (a low-medium-risk subjects group) presented no DVT at all after 7 to 12 hour flights. This may suggest that when passengers are aware of the risk, they spontaneously take appropriate preventive measures and hence avoid the problem.

Conclusion

While the economy class syndrome became better known in 1988 after the description of 5 cases of deep vein thrombosis occurring in aeroplanes, the problem of the risk of deep vein thrombosis while/or following sitting during travel goes far beyond this anecdotal evidence. There have been many cases reported in the literature, but it is likely that most go unrecognized.

Travel is a probable and long underestimated cause of DVT/PE.

In many modern epidemiological studies, about half of DVTs and PEs remain asymptomatic. In a way, it is reassuring to note that, alongside various congenital predispositions which have been discovered in recent years, new acquired factors such as travel have been identified. These factors reduce the number of cases of DVT/PE with no rational explanation. What now remains to be determined is the best prevention strategy.

References

1. Cruickshank JM, Gorlin R, Jennett B (1988) Air travel and thrombotic episodes: the economy class syndrome. Lancet ii: 497-498
2. Alberty-Ryoppy A, Juntunen J, Salmi T (1985) Femoral neuropathy following anticoagulant therapy for "economy class syndrome" in a young man. Acta Chir Scand 151: 643-645
3. Virshow R (1856) Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Meidinger, Frankfurt, p 227
4. Simpson K (1940) Shelter deaths from pulmonary embolism. Lancet ii: 744
5. Homans J (1954) Thrombosis of the deep leg veins due to prolonged sitting. N Engl J Med 250: 148-149
6. Ribier G, Zizka V, Cysique J, Donatien Y, Glaudon G, Ramialison C (1997) Venous thromboembolic complications following air travel. Retrospective study of 40 cases recorded in Martinique. Rev Med Intern 18: 601–604
7. Eklof B, Robert L, Kistner RL, Masuda EM, Sonntag BV, Wong HP (1996) Venous thromboembolism in association with prolonged air travel. Dermatol Surg 22: 637-641
8. Beighton PH, Richards PR (1968) Cardiovascular disease in air travellers. Br Heart J 30: 367-372
9. Sarvesvaran R (1986) Sudden natural deaths associated with commercial air travel. Med Sci Law 26: 35-38
10. Ferrari E, Baudouy M, Cerboni P, et al. (1997) Clinical epidemiology of venous thromboembolic disease. Results of a French Multicentre Registry. Eur Heart J 18: 685-691
11. Ferrari E, Chevallier T, Chapelier A,Baudouy M (1999) Travel as a risk factor for venous thromboembolic disease: a case-control study. Chest 115: 440–444
12. Samama M-M (2000) An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius Study. Arch Intern Med 160: 3415-3420

13. Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Büller H (2000) Travel and the risk of venous thrombosis. Lancet 356: 1492–1493
14. Arya R, Barnes JA, Hossain U, et al. (2002) Long-haul flights and deep vein thrombosis: a significant risk only when additional factors are also present. Br J Haematol 116: 653-654
15. Dimberg LA, Mundt KA, Sulsky SI, et al. (2001) Deep venous thrombosis associated with corporate air travel. J Travel Med 8: 127-132
16. Giangrande PLF (2002) Air travel and thrombosis. Br J Haematol 117: 509-512
17. Rege KP, Bevan DH, Chitolie A, et al. (1999) Risk factors and thrombosis after airline flight. Thromb Haemost 81: 995-996
18. Gallus AS, Goghlan DC (2002) Travel and venous thrombosis. Curr Opin Pulm Med 8: 372-378
19. Bagshaw M (2001) Traveller's thrombosis: a review of deep vein thrombosis associated with travel. Aviat Space Environ Med 72: 848-851
20. Ansell JE (2001) Air travel and venous thromboembolism – is the evidence in? N Engl J Med 345: 828-829
21. Egermayer P (2001) The "economy class syndrome": problems with the assessment of risk factors for venous thromboembolism. Chest 120: 1047-1048
22. Hirsh J, O'Donnell MJ (2001) Venous thromboembolism after long flights: are airlines to blame? Lancet 357: 1461-1462
23. Arfvidsson B, Elkof B, Kistner RL, et al. (2000) Risk factors for venous thromboembolism following prolonged air travel. Hem/Onc Clin N Am 14: 391-400
24. Scurr JH, Machin SJ, Bailey-King S, et al. (2001) Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. Lancet 357: 1485-1489
25. Belcaro G, Geroulakos G, Nicolaides AN, et al. (2001) Venous thromboembolism from air travel: the LONFLIT Study. Angiology 52: 369-374
26. Belcaro G, Cesarone MR, Shah SSG, et al. (2002) Prevention of edema, flight microangiopathy and venous thrombosis in long flights with elastic stockings. A randomized trial: the LONFLIT 4 Concorde Edema-SSL Study. Angiology 53: 635-645
27. Cesarone MR, Belcaro G, Nicolaides AN, et al. (2002) Venous thrombosis from air travel: the LONFLIT3 study. Prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. Angiology 53: 1-6
28. Schwarz T, Langenberg K, Oettler W, et al. (2002) Deep vein and isolated calf muscle vein thrombosis following long-haul flights: pilot study. Blood Coag Fibrino 13: 755-757
29. Lapostolle F, Surget V, Borron S, et al. (2001) Severe pulmonary embolism associated with air travel. N Engl J Med 345: 779-783
30. Lapostolle F, Borron SW, Surget V, Sordelet D, Lapandry C, Adnet F (2003) Stroke associated with pulmonary embolism after air travel. Neurology 60: 1983-1985
31. Eschwège V, Robert A (1996) Strikes in French public transport and resistance to activated protein C. Lancet 347: 206(Letter)
32. Wright HP, Osborn SB (1952) Effect of posture on venous velocity measured with 24NaCL. Br Heart J 14: 325-330
33. Carruthers M, Arguelles AE, Mosovich A (1976) Man in transit: biochemical and physiological changes during intercontinental flights. Lancet I: 977-981
34. Simons R, Krol J (1996) Jet "leg", pulmonary embolism, and hypoxia. Lancet 348: 416 (Letter)
35. Gertler JP, Perry L, L'Italien G, et al. (1993) Ambient oxygen tension modulates endothelial fibrinolysis. J Vasc Surg 18: 939-946
36. Bendz B, Rostrup M, Sevre K, Andersen T, Sandset PM (2000) Association between acute hypobaric hypoxia and activation of coagulation in human beings. Lancet. 356: 1657-1658
37. Zornberg GL, Jick H (2000) Antipsychotic drug use and risk of first time idiopathic venous thromboembolism: a case control study. Lancet 356: 1219-1223

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