Air Travel-Associated Venous Thromboembolism

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Key Words

Thromboembolism · Protein C · Thrombophilia · Mutation · Prothrombin · Hypoxia

Abstract

Long-distance air travel is increasing and cases of venous thromboembolism (VTE) following air travel have attracted both considerable public attention and legal claims against airlines. VTE is a common disorder worldwide with a notably high incidence in older individuals. Many biochemical factors that lead to, or accentuate, thrombus formation are associated with increased risk of VTE. These factors include thrombophilia, activated protein C resistance and factor V Leiden, prothrombin gene mutation, antiphospholipid antibodies, protein S and protein C deficiencies, and methylene tetrahydrofolate reductase polymorphism and homocysteinemia. Individual physical characteristics including age, weight and height are significant for personal risk of VTE as are other factors such as use of oral contraceptives in women. In the case of air travel-related venous thrombosis, superimposed upon these individual factors are the environmental factors directly related to air travel. Travel-related factors include stasis associated with prolonged periods of immobility, physiological stresses resulting from ex-

posure to the cabin environment (low humidity and hypoxia) in long-haul flight and other in-flight factors. It is suggested that passenger behavior (movement, avoidance of dehydration and of alcohol) and appropriate pharmacological prophylaxis for high-risk travelers can reduce the likelihood of VTE. Physical prophylaxis (use of compression stockings or in-flight exercise devices) may also be of general benefit to passengers. It is recommended that airlines become more proactive in educating passengers concerning the dangers of VTE and in promoting passenger actions that can reduce risk. Airlines should also work to avoid cramped seating conditions (seat size and pitch) that contribute to prolonged immobility. Governments and regulatory authorities should mandate the provision of adequate seating conditions and a good cabin environment and should support studies that will define risks and determine the efficacy of protocols to minimize dangers of VTE. Increased long-haul air traffic and an aging population suggest that travel-related VTE may present a growing healthcare threat and has highlighted a need for additional biomedical research into the causes and potential solutions to this problem.

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Introduction

Venous thromboembolism (VTE) is a common disorder worldwide. The estimated annual incidence of symptomatic thromboembolism is 117 cases per 100,000 people [1] or more than 250,000 patients each year in the United States. The incidence is age-dependent, increasing from zero in children to less than 1 per 10,000 in young adults and 3–5 per 10,000 in individuals over the age of 60 with additional increments with each additional decade [2]. With a large proportion of the US population entering the older age-group, VTE will become an increasingly important national health problem [1]. Venous thrombosis commonly develops in the deep veins of the leg (calf-vein thrombosis and proximal-vein thrombosis involving the popliteal, femoral or iliac veins) or the arm. Pulmonary emboli are sequelae from thrombi in the deep veins of the leg in 90% or more patients. Deep-vein thrombosis (DVT) and/or pulmonary embolism are referred to as VTE. Rudolf Virchow [3] was the first to recognize that VTE may be precipitated by venous stasis secondary to immobility.

Homans [4] first described in 1954 the possible association between long-distance air travel and VTE and reported 5 cases of DVT after prolonged sitting. He also described the association between car travel and VTE. Later, Symington and Stack [5] also reported thromboembolic events following long-distance travel and referred to the problem as 'economy class syndrome' [5]. Reports of pulmonary embolism as a second leading cause of travel-related deaths at London's Heathrow airport [6] raised much concern and resulted in a series of reports linking prolonged air travel and VTE [7–12]. With the increase in international air traffic, VTE following long-distance travel has been widely recognized and further documented in the literature; Ferrari et al. [9] reported that long-distance travel was associated with an increased risk for thromboembolic disease. Samama [13] reported an epidemiologic study of risk factors for DVT in medical outpatients. Kraajenhagen et al. [14] reported on travel and risk of venous thrombosis. In this study, the number of events and subjects exposed to long-distance travel were small and could not confirm an association between air travel and VTE. Scurr et al. [15] reported on the results of a randomized trial on the frequency and prevention of symptomless DVT and long-haul flights. The results of biased ultrasonographic assessments were questioned [15]. Belcaro et al. [16] published on venous thromboembolism from air travel – the LONFLIT study. In the LONFLIT 1 study, 355 patients at low risk for DVT and

389 patients at high risk were studied. After a 12.4-hour economy class flight, no events were recorded in the low-risk group but in the high-risk group, 11 patients had DVT (2.8%). In the LONFLIT 2 study, of the 833 subjects, 422 were randomized as control subjects and 411 used below-knee stockings as a prophylactic measure against VTE. Parsi et al. [17] reported on 'Traveller's venous thromboembolism', a review of the world literature which encompassed a survey of the world airlines and presented an Australian perspective. Lapostolle et al. [18] reported on severe pulmonary embolism associated with air travel, recording 56 cases in 135.3 million passengers passing Charles de Gaulle airport in France. The frequency of embolism in long-haul passengers (>5,000 km) was 150 times higher than the incidence in passengers traveling shorter distances. Kline et al. [19] reported that the incidence of fatal pulmonary embolism immediately after transatlantic air travel to the United States was less than 1 in a million.

Press reports of 'economy class syndrome' have not only attracted public attention but have created tremendous anxiety in the minds of airline officials. Many lawsuits have been filed against the industry concerning their failure to warn passengers of the potential health risks, including VTE, of long-distance air travel.

An International Consensus View of VTE and Air Travel

Alerted by the media, the World Health Organization (WHO) recently convened a meeting of experts (WHO Consultation Meeting, Geneva, Switzerland, March 12–13, 2001, Chairman: Dr. F. Peccaud, Lausanne) with the intention to: (a) review and synthesize the information on air travel-related venous thrombosis (ATVT); (b) define the extent of the problem; (c) identify priority areas of research to find possible solutions if a problem exists, and (d) try to reach a consensus of pragmatic strategies for prevention based on currently available evidence [20].

The experts agreed: (a) that an association probably exists between air travel and venous thrombosis; (b) such an association is likely to be small and mainly affects passengers with additional risk factors for venous thromboembolism; (c) similar links may exist for other forms of travel; (d) available evidence does not permit an estimation of actual risk, and therefore public health recommendations cannot be made at the present time.

The representatives of the airlines agreed that: (a) an association between venous thrombosis and travel in general probably exists; (b) there are insufficient data on which to make recommendations; (c) airlines and the

International Air Transport Association (IATA) are consequently committed to support further research.

It was the unanimous view of the participants that these studies should be undertaken as soon as possible under the auspices of WHO and supported by an independent scientific committee in close collaboration with IATA and International Civil Aviation Organization (ICAO). The priorities for research were suggested in three areas and protocols for funding were drawn up:

(1) A set of multicenter, international, epidemiological studies including a large prospective cohort study examining hard clinical endpoints to answer the following questions: Is there an association and if so, what is the absolute risk? What is the size of the problem? Studies on aircrew and cabin staff, as well as populations from multinational companies are planned.

(2) A set of special small-scale studies seeking intermediate endpoints and/or specific questions to groups of volunteers examining isolated independent environmental and behavioral risk factors. These studies will include physiopathological studies using hypobaric chambers.

(3) A set of interventional studies to assess preventive measures on the occurrence of ATVT with standardized diagnostic methods, involving passengers in experimental well-controlled studies.

Venous Thrombosis: Factors Contributing to Thrombosis Risks

Individual Factors

The pathogenesis of DVT as proposed by Virchow [3] is based on three groups of factors ('Virchow's triad'), namely, hypercoagulability, stasis and venous injury. More than one personal risk factor is frequently present in an individual case. Individual risk factors may be potentiated by travel-related factors and thus place certain passengers at higher risk.

Biochemical Factors: Patient-Related Biochemical VTE Risk Factors for Hypercoagulability

These include: thrombophilia; activated protein C resistance, inherited (factor V Leiden); prothrombin gene mutation (G20210A); antiphospholipid antibodies; protein S and protein C deficiencies, and methylene tetrahydrofolate reductase (MTHFR) polymorphism and hyperhomocystinemia MTHFR A1298C and C677T. The conditions have established association with VTE and have

been recorded in individuals suffering from travel-related thromboses.

Thrombophilia. The role of thrombophilia in the pathogenesis of travel-related VTE was studied by Lord and McGrath [21] in 1993. Thrombophilia was identified in 72% of patients with travel-related VTE [22, 23]. The major defects associated with familial thrombophilia are: activated protein C resistance caused by Arg 506 to Gln mutation (factor V Leiden), prothrombin polymorphism (G20210A) causing an elevated prothrombin level, hyperhomocystinemia, protein C deficiency, protein S deficiency, antithrombin deficiency and elevated factor VIII levels.

Activated Protein C Resistance. Activated protein C resistance, detected in 47% of the patients with travel-related VTE [22–24], was the most common thrombophilic abnormality. About 34% of all patients showed a mutation in factor V gene leading to a G → A substitution at the nucleotide position 1691. As a result of this substitution of glutamine for arginine at amino acid position 506 (FV R506Q), the factor V becomes resistant to proteolytic downregulation by activated protein C (30% heterozygous and 4% homozygous) [23]. Activated protein C resistance without factor V Leiden mutation is a risk factor for VTE [25] and was observed in 15% of the patients with travel-related VTE [23]. Rees et al. [26] analyzed 3,380 chromosomes (1,690 unrelated individuals) from 24 populations for the presence of factor V Leiden. The allele frequency was reported to be 4.4% in Europe, with the highest prevalence in Greeks (7%) and 0.6% in Asia Minor. Factor V Leiden mutations were not found in any of the chromosomes from Africa, South East Asia, Australasia and America [26]. Dzimiri and Meyer [27] did not concur with the report by Rees et al. [26] and reported the distribution of factor V Leiden in Saudi Arabia (5 hetero/200, 2.5%). They screened 200 unrelated healthy Saudi young men visiting the blood donor clinic at King Faisal Specialist Hospital and Research Center in Riyadh, Saudi Arabia. Five (2.5%) of 200 individuals had the A → G mutation at position 1691 detected by Mn/1 digestion confirmed by direct sequencing [27]. Dahlbach [28] reported the frequency in the range of 3–7%.

Prothrombin G20210 Gene Polymorphism. First reported by Poort et al. [29] in 1996, replacement of G by A at nt 20210 in the 3'-untranslated region of the prothrombin gene increases translation without altering the transcription of the gene, resulting in the elevated synthesis and secretion of prothrombin by the liver. This increased synthesis and secretion of prothrombin contributes to increased thrombotic risk by causing increased thrombin

generation that can activate thrombin activatable fibrinolytic inhibitor resulting in fibrinolytic deficit. The A20210 allele is present in 5–7% of VTE patients and is the second most common genetic risk factor for VTE [29–31]. A combined mutation of factor V Leiden and prothrombin gene 20210 is associated with a higher risk of VTE [32–38]. In a travel-related VTE study, 24% of patients were heterozygotes for this mutation [23], 11% also had a factor V Leiden mutation, 2% had associated protein S deficiency and 36% of the premenopausal women on oral contraceptive agents showed this mutation.

Antiphospholipid Antibodies. Antiphospholipid antibody syndrome is an acquired disorder characterized by thrombotic manifestations together with laboratory evidence of autoantibodies. These antibodies recognize anionic phospholipid-protein complexes, and are found in 1–5% of the general population and in 50% of patients older than 80 years [36, 37] of which about 30% of the patients were reported to have thrombosis [38, 39]. Antiphospholipid antibodies were found in 15–20% of all VTE cases. Among the travel-related VTE events 8% of patients had antiphospholipid antibodies, 2% lupus anticoagulants and 6% anticardiolipin antibodies.

Protein S and Protein C Deficiencies. Protein S is a vitamin K-dependent glycoprotein, synthesized by hepatocytes, neuroblastoma cells, kidney cells, testis, megakaryocytes, and endothelial cells. It is found in α -granules of platelets and is a nonenzymatic cofactor of activated protein C in the inactivation of Va and VIIa [40–45]. Inherited in an autosomal dominant manner, protein S deficiency accounts for only 1% of thrombotic events and 7% among patients with travel-related VTE [22, 23]. Patients with protein S deficiency may also be predisposed to arterial thrombosis [46]. Protein C, a zymogen, synthesized in liver, is a vitamin K-dependent inhibitor of factors Va and VIIa. Hereditary protein C deficiency, an autosomal dominant disorder, is associated with a 7-fold increased risk of VTE [47, 48]. Among patients with travel-related VTE, 4.8% of patients had deficiency of protein C [23]. Protein C and S levels are reduced by vitamin K deficiency, anticoagulation with warfarin and liver failure [49]. The levels of protein S are altered by age, oral contraceptives and pregnancy and are falsely low in the presence of factor V Leiden [49].

Methylene Tetrahydrofolate Reductase (MTHFR) Polymorphism and Hyperhomocystinemia. Hyperhomocystinemia is commonly associated with VTE and arterial thrombosis. In a travel-related VTE study, 44% (18% homozygous and 26% heterozygous) showed a mutation in the MTHFR gene. Heterozygosity was not considered a

risk factor for VTE [22]. The most common known genetic cause of hyperhomocystinemia involves polymorphism of the MTHFR gene, ntC677T and A1298C. MTHFR catalyzes the reduction of methylene tetrahydrofolate to methyl tetrahydrofolate with folate acting as a cofactor. Methyl tetrahydrofolate is important in the remethylation pathway of homocysteine where dietary folate and vitamin B₁₂ are also required. Acquired hyperhomocystinemia may be due to chronic renal failure, B₁₂, B₆ and folate deficiency states or may be induced by cyclosporine and methotrexate treatment.

Combined Genetic Defects. Deda et al. [50] reported on combined genetic defects of protein S deficiency, factor V Leiden mutation and a high level of factor VIII in a 10-year-old Turkish boy with ischemic stroke.

Physical Factors Associated with VTE Risks for Individuals

Age. The risk of VTE increases with age and the incidence is 1 in 100 for patients over the age of 75 years [51].

Weight and Height. Obesity has an association with the development of postoperative VTE and in a study with travel-related VTE [52], 58% of patients were considered overweight [21, 22]. Spontaneous DVT has been reported in the legs of tall men and it is postulated that the greater vein length may increase the difficulty of venous return to the vena cava thus predisposing an individual to stasis and thrombosis [53].

Other Factors Associated with VTE Risks for Individuals

Oral Contraceptives. Oral contraceptives increase the risk of VTE [54]. In a travel-related VTE study, 73% of the premenopausal women and 53% of the postmenopausal women were taking oral contraceptives [23]. Government of UK guidelines state that people with a history of thrombosis and who have been taking hormone replacement therapy are among those at greater risk of suffering from DVT.

Additional Risk Factors. A medical history including previous DVT or pulmonary embolism, recent surgery or malignancy correlates with increased risk of VTE.

In-Flight Factors and VTE Risks

The particular environment to which passengers are exposed during long-haul air travel may potentiate individual risk factors for development of DVT.

Venous Stasis

Immobility, regardless of cause, results in decreased venous return and stasis. When blood flow becomes sluggish and tends to stagnate, venous thrombi are formed in the valve pockets. Venous stasis is itself a principal precipitating factor for DVT [55]. Advanced age and immobilization further increase the frequency of thrombosis. Venous stasis is associated with impaired fibrinolysis and activation of coagulation [56, 57], increased fluid retention, causing swelling in the legs [58] and increased erythropoietin levels [59].

Physiological Stress

Dehydration and Hemoconcentration Resulting from Reduced Humidity. A fall in cabin relative humidity (RH) from 47 to 11% occurs within 30 min of takeoff [60]. This low RH may contribute to excessive fluid loss, hemoconcentration and dehydration. Decreased urine output with an increased osmolality and the resulting hemoconcentration contributes to VTE [61]. Simons and Krol [62] demonstrated the increase in mean plasma and urine osmolality of patients exposed to simulated flight at an altitude of 8,000 feet and 8–10% RH.

Hypoxia and Altitude. Most commercial aircraft reach an altitude of 26,000–42,000 feet (50,000–60,000 feet for Concorde), at which altitude the atmospheric pressure, which was 760 mm Hg at ground level, decreases to 176 mm Hg. Since it is impossible to maintain the cabin pressure at a value equivalent to ground level, aircraft are pressurized so that the cabin pressure is maintained at the equivalent of around 5,000–8,000 feet altitude regardless of the cruising altitude [62]. The arterial oxygen pressure (98 mm Hg at sea level) falls with increasing altitude [63, 64]. Simulated flight experiments performed in hypobaric chambers with an inside ambient pressure of 75.8 kPa (equivalent to cabin altitude of 8,000 feet) showed that the alveolar pO_2 drops to only 59 mm Hg and mean oxygen saturation reaches 90% after 30 min of exposure [65, 66]. Passengers may experience relative hypoxia, especially during takeoff and if the passengers have preexisting respiratory or cardiac problems, this change would be troublesome. Hypoxia can cause activation of coagulation and enhanced expression of plasminogen activator inhibitor 1, thereby suppressing fibrinolysis [11, 12, 67]. Short-term exposure to high altitude causes coagulation activation and inhibition of fibrinolysis [68]. Bendz et al. [69] demonstrated association between acute hypobaric hypoxia and activation of coagulation in humans [70, 71]. It was also reported that low molecular weight heparins prevent activation of coagulation in a hypobaric chamber

[72]. It would be interesting to observe if there is any enhanced expression of thrombin activatable fibrinolytic inhibitor. Hypoxia may also cause endothelial activation and injury. Release of endothelium-derived relaxing factor can cause relaxation of venous walls resulting in venous stasis [12]. Effects of sleep can influence hypoxia. Lower oxygen saturations of 80% at cabin altitudes of 8,000 feet were observed in individuals who were sleeping during a flight [62]. Drowsiness, immobility, cramped conditions, and low cabin pressure leading to distension of the abdomen can limit the normal movements of the diaphragm. Once the passenger breathes normally, the oxygen saturation level increased [62]. Hypoxemia also leads to vasodilatation; increased capillary permeability in combination with immobility results in edema.

Other Factors

Radiation Exposure. During flights the pilots, cabin crew and passengers are exposed to increased levels of cosmic radiation which primarily consists of neutrons and gamma rays. Higher levels are experienced at the highest altitudes and in the polar regions [73]. A direct link between cosmic radiation and thrombosis has so far not been established.

Related Conditions: Air Travel and Risk of Arterial Thrombosis. Current reports on flying and thrombosis mainly refer to venous thromboembolic complications. However, individuals with arterial diseases are also predisposed to symptomatic problems after extended air travel. Stress, and blood flow alterations contribute to ischemic events. Therefore, individuals with diabetic arteriopathy, advanced atherosclerosis and microangiopathic disorders are predisposed to complications. Although a systematic study on the prevalence of arterial thrombosis is not available, the reported incidence of acute coronary syndrome and myocardial infarction points in this direction. It is for this reason that some airlines have outfitted aircraft with defibrillators.

Solutions: Approaches to Reducing Risks of Travel-Related Thrombosis

Reduction of VTE risks for the traveling public must involve both individual action by passengers and the provision of good travel conditions by the airline carriers. All aspects of airline safety are subject to strict control and regulation by governmental agencies and international authorities and organizations.

Individual Action to Reduce VTE Risk

Behavior Modifications

Mobility and Exercise. Passengers are usually advised to move about and exercise especially during long flights in order to improve circulation [74, 75]. Passengers should heed this advice. However, if passengers do not get any opportunity to move about due to turbulence, they may remain seated and perform dorsiflexion of the feet to improve circulation. Wright and Osborn [76] have shown that venous velocity was doubled after vigorous dorsiflexion of the foot. Sochart and Hardinger [77] have recently demonstrated that all passive or active movements (ankle dorsiflexion and plantar flexion, subtalar inversion and eversion and a combination) resulted in an increase in mean and peak blood velocities in common femoral veins. Mechanical devices to enhance foot and leg movements by passengers while seated have been developed.

Fluid Balance. Passengers should drink plenty of fluids and avoid alcohol or diuretics, unless medically advised.

Prophylaxis

Pharmacological Prophylaxis

Low molecular weight heparins (LMWHs), antiplatelet agents and warfarin are generally used for the prophylaxis of VTE. LMWHs have several advantages when compared to unfractionated heparin, including higher bioavailability, longer half-life and no need for laboratory monitoring. LMWHs have been shown to be effective for the prevention of VTE in high-risk patients who undergo hip or knee surgery or in patients with major trauma or acute spinal cord injury [78]. Antiplatelet drugs were found to have much less protective effect than anticoagulant agents [79]. The use of aspirin to prevent VTE is controversial and hence is not recommended [17].

Mechanical Prophylaxis

Graduated Compression Stockings. These stockings increase the venous blood flow velocity. In two separate meta-analyses, 9.3 and 11.2% of postoperative patients experienced DVT when compared to 24.5 and 27% in the placebo groups, respectively [80, 81]. Marshall and Dormandy [82] found a 60-ml increase in lower limb volume during a flight from Frankfurt to Kyoto, when no preventive measures were undertaken. In one study, Lowe et al. [83] demonstrated the efficacy of 25–32 mm Hg graduated-compression stockings for prevention of venous

edema during a 14.4-hour night flight. In a recent study (LONFLIT 2), Belcaro et al. [16] enrolled 833 subjects, 422 randomized as control subjects and 411 used below-knee stockings. After an average flight duration of 12.4 h, 4.5% of the control subjects and only 0.24% of the subjects using below-knee stockings developed DVT (thrombosis detection based on ultrasound scans), showing a statistically significant difference. Thus, it was observed that subjects wearing stockings had 18.75 times lower incidence of DVT compared to the controls. It was concluded that long-haul flights were associated with DVT in 4.5% of the high-risk patients and that below-knee stockings were beneficial in reducing the incidence of DVT [16]. Battery-driven intermittent compression pumps that can give foot or calf compression during the flight have also been developed.

Approaches by Organizations to Combat Travel-Related VTE

Airlines

Airlines should consider providing passengers with information related to long-distance flight and its association with development of VTE together with a description of the preventive measures that can be taken in order to minimize risk. This information could be provided on a card similar to the one provided for aircraft safety information. If this information is also given at the time of purchase of the tickets, or at least before the flight, the passengers could have enough time to discuss this matter with their physicians and receive additional safety tips. Passengers with severe individual risk factors, such as previous DVT or recent surgery, could then arrange for specific prophylaxis under medical direction. Airlines should also work to make available more leg space and thus facilitate leg mobility for passengers during long-haul flights. Passengers should be encouraged to move out of their seats and either exercise or at least walk a few steps, whenever it is safe to do so. Passengers should be encouraged by cabin staff to drink plenty of fluids during the flight and to avoid alcohol.

Governments and Regulatory Authorities

The WHO in collaboration with ICAO and IATA are planning large prospective studies to further establish the importance of travel and travel-related conditions in the development of venous thromboembolic complications. Clinical trials and databases to record the incidence of thrombosis in patient groups with both arterial and ve-

nous thrombosis may be helpful. Investigation of improved laboratory methods to predetermine the risk profile of travelers may be of general utility. An optimum interseat distance should be established in order to facilitate adequate leg mobility for passengers.

Conclusions

Public and professional understanding of travel-related venous thromboembolic complications and close interactions of physicians, health care authorities and national and international aviation authorities would help to provide safer long-distance air travel.

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