



## Long Distance Flights and the Risk of Venous Thromboembolism – A Real Threat or Just Another Flight Hysteria?

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Each year, more than one billion people travel by air worldwide [1] and the vast majority of them complete their flights safely. However, a small number of passengers will experience an acute illness during or soon after the flight. The true incidence of in-flight medical emergencies is unknown as many airlines either do not keep records or do not make them public. The Seattle-Tacoma International Airport reported that 1 of every 39,000 passengers has experienced an in-flight medical emergency [2]. The death rate during flight for the years 1977–1984 was reported as 1 death per 3.25 million passengers [3]. In 1986, a study from London's Heathrow Airport found that 18% of 61 sudden deaths among long-distance flight passengers were due to pulmonary embolism. This made PE the most common cause of such deaths after ischemic heart disease [4].

The relationship between venous thromboembolism and prolonged air travel was first described by Homan in 1954 [5]. Since then many reports have suggested that people who fly long distances have a higher risk of deep vein thrombosis and pulmonary embolism [6,7]. The most famous of all patients to suffer flight-related VTE was the late former president of the United States, Richard M. Nixon, who developed a major blood clot in his iliac vein during a tour of the Middle East in 1974, followed by a few episodes of almost fatal pulmonary embolism.

The exact risk for any given passenger to develop VTE during a long-distance flight is unknown. Based on the number of reported cases it may be concluded that flight-related VTE is quite rare. With the increased volume of air transportation during the last decades, more patients have been diagnosed and public attention has been alerted. The term "Economy Class Syndrome" was coined for this condition [4,6,7], which gained headlines in *Time* magazine.

In spite of the small amount of available data, numerous studies

report the main risk factors for air travel-induced VTE. In the only case-control study, Ferrari et al. [8] found that prolonged travel (air, train or car) was associated with an increased risk of venous thromboembolism.

It has been postulated that during air travel, deep vein thrombosis may occur as a result of venous stasis in the lower limbs brought on by cramped conditions. The association between sitting in cramped conditions and death from PE has been known since World War II. The London population, which spent many hours in cramped air-raid shelters during the London Blitz, suffered from a marked increase of venous thrombosis and pulmonary emboli [9].

Despite some recent innovations, the modern airline seat in the economy class remains a modified instrument of torture. Sitting in an economy class seat for hours does not differ substantially from sitting in the bombed World War II shelters in London. The prolonged sitting in the same recumbent posture and relative immobilization reduces calf pump function and flow through the deep veins of the lower limb during a long-distance flight. It was shown that venous flow velocity was approximately halved when the subject is sitting as opposed to being supine, thus causing filtration of fluid from the circulation and swelling of the legs and feet [10]. In addition to ill-designed cramped seats, other air cabin-related risk factors increase the risk for flight-related VTE. At the high altitude of the typical operational flight level of 35,000 feet, the pressurized flight cabin creates a microcosmos in which a number of factors influence Virchow's known triad (endothelial lesion, venous stasis, and hypercoagulability). Low air pressure, low humidity, relative hypoxia, and dehydration are the most prominent. The low cabin humidity of 8–12% increases fluid loss, which leads to dehydration. Inadequate fluid intake, the diuretic effect of the consumption of alcohol that is served free of charge, and the dependency distribution of fluids leading to swollen feet and legs further exacerbate this condition. Moreover, during long-distance flights, passengers are trapped in their seats by the trolleys in the aisle, illuminated signs that instruct the passengers to wear security seat belts at all times, and curtains that divide the aircraft compartments.

PE = pulmonary embolism

VTE = venous thromboembolism

The relative hypoxia caused by a decrease in blood oxygen tension at the lower cabin pressures maintained at high altitudes may also contribute to the initiation of venous thrombosis in passengers [11,12]. The passenger experiences hypoxia (alveolar pO<sub>2</sub> drops to only 59 mmHg (as compared to 107 mmHg at sea level in a person with normal lungs). Accumulated data suggest that hypoxia decreases endothelial cell fibrinolytic activity and induces generation of endothelium-derived relaxing factor [13]. As a result, decreased fibrinolysis enhances hypercoagulability; relaxation of the venous wall leads to decreased flow velocity and stasis, thus putting passengers at greater risk of developing venous thromboembolism. Advanced age, obesity, recent surgery, malignancy, heart failure, and use of estrogen hormone are only some of the risk factors that, together with the aforementioned specific cabin-related risk factors, have a key role in the genesis of flight-related VTE.

Certain passengers with genetic abnormalities leading to hypercoagulability and thrombophilia are at higher risk than others for flight-related VTE. In a recent study, procoagulant blood abnormalities were found in about half of those with flight-related clinically significant VTE [14]. The most common genetic abnormality is the factor V Leiden mutation, which is present in 4–6% of the general population, and is associated with activated protein C resistance [15]. Heterozygosity for this mutation has a five to tenfold increased risk for venous thromboembolism, while the risk among homozygous individuals increased by eighty-fold. Another mutation, a guanine to adenine nucleotide substitution at nucleotide position 20210 in the prothrombin gene, is associated with higher prothrombin levels and a greater risk for VTE [16]. A mutated 5-methyltetrahydrofolate reductase, when associated with elevated plasma homocysteine levels, is a confirmed risk factor for VTE [17]. However, to date, there have been no prospective reported studies indicating the percent of air travelers with a mutated allele who experience a flight-related VTE.

In 1996 Eklof et al. [6] reported 44 cases of VTE during or after air flights of 5–17 hours at Honolulu International Airport. Most of the patients developed symptoms during the first 24 hours after the start of the flight. In some, the first symptom occurred during the flight. Of the 44 patients studied, the identified risk factors were: a history of DVT (34%), presence of a related chronic disease or malignancy (25%), hormone therapy (16%), recent lower limb surgery (11%), and recent surgery or femoral catheterization (9%). Only 5% of the total group did not have any apparent predisposing risk factors. Another study from Hawaii reported that 17% out of a sample of 254 patients admitted to hospital with a diagnosis of DVT or PE had developed symptoms during or after a flight [14]. The affected patients were predominantly middle-aged or elderly and the flight time varied between 5 and 17 hours.

To reduce the risk of the "Economy Class Syndrome," simple precautions should be taken. First of all, cabin-related risk factors that cause hypercoagulability and stasis can be corrected by frequent leg and body exercises and regular walks. Reserving a seat on the aisle is suggested, as there is more leg-stretch room and easy access to the aisle in order to walk around. Individuals should change their positions frequently and engage in numerous

stretching exercises. Excessive alcohol consumption should be avoided. To avoid dehydration, regular non-alcoholic beverages should be consumed (at least 1 L per 5 hours of flight). A number of publications have suggested that increased fluid intake, calf exercise, and avoidance of alcohol reduces the risk of thromboembolic phenomena [7,18,19].

Patients with intrinsic risk factors should use therapeutic compression stockings to reduce swelling of the legs and increase venous flow velocity. A recent prospective study [20] evaluated the efficacy of elastic stocking in prevention of flight-related VTE. A surprisingly large proportion (10%) of the control group (without elastic compression stockings) developed symptomless DVT following long-distance flights (median 24 hours), while none was detected in the stocking group [20]. In this study the prevalence of gene mutations (factor V Leiden or prothrombin gene mutation) was 19% among the travelers who developed superficial or deep vein thrombosis compared to 7% in the rest of the passengers.

Patients with a history of DVT, chronic disease, malignancy, recent surgery or vascular interventions should consider prophylaxis with low molecular weight heparin to prevent DVT. Some authors have also advised taking an aspirin each day for a few days prior to a long flight unless otherwise contraindicated [7]. However, the use of aspirin as a preventive measure is controversial according to the latest consensus guidelines [21]. Another way that high risk patients can reduce the risk of venous thromboembolism during air travel is through the use of a foot pump. This pump simulates a physiologic pumping mechanism in the sole of the foot, which is activated by the flattening of the plantar arch on weight-bearing, and was found to maintain venous circulation as effectively as does normal walking [22].

In summary, flight-related venous thromboembolism is a rare but distinct and real danger. Even though a few reported cases of DVT/PE following air travel have occurred in passengers with no previous medical history, certain risk factors are associated with the development of air travel-related VTE. For individuals with preexisting risk factors, long trips in cramped conditions by air do carry a risk of DVT/PE. In the future, physicians should have their patients take an individual risk assessment before long-distance travel. Those passengers who are low risk should not use prophylaxis, but should be told to drink enough fluids and occasionally stretch their legs. Passengers who are classified as high risk should consider taking low molecular weight heparin during the flight. The use of foot pumps may be beneficial if this method eventually becomes available. To decrease the prevalence of this problem, reasonable and simple measures could be implemented by the airlines. For example, they could make passengers aware of the dangers of dehydration during flight, promote the consumption of non-alcoholic beverages and discourage ingestion of alcoholic beverages. Airlines could also increase the space between passengers to give them more room to stretch their legs during the flight – though it is hard to believe they will do so due to economic considerations. Information leaflets dedicated to travelers' education about flight-related VTE and its prevention can be a simple and effective first step.

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## Capsule

### The signature of stem cells

Are there genes that characterize various sets of stem cells? Ivanova et al. (*Science* 2002;298:601) and Ramalho-Santos et al. (p. 597) used transcriptional profiling of mammalian embryonic and adult stem cells to identify genes that are common among hematopoietic stem cells, embryonic stem cells, and neural stem

cells. These subsets of genes may provide stem cells with the ability to self-renew, to generate differentiated cells, or to do both, and hence represent, according to the authors, "stemness" or a "stem cell molecular signature."

## Capsule

### Sleep apnea linked to decreased libido

Male patients who suffer from obstructive sleep apnea – the inability to breathe properly during sleep – produce lower levels of testosterone, resulting in decreased libido and sexual activity, according to scientists at Israel's Technion Institute of Technology. While previous studies reported decreased libidos in male sleep apnea patients, they were unable to establish a scientific link. Now a recent study (*J Clin Endocrinol Metab* July 2002), using a different methodology, confirmed this finding. Earlier studies had measured testosterone levels once after awakening, whereas

in the present study subjects were admitted to the Technion Sleep Center for an entire night and were fitted with electrodes and catheters. The subjects – sleep apnea patients and age and weight-matched controls – were monitored between 7 p.m. and 7 a.m. with blood samples collected every 20 minutes. At 10 p.m. the lights were turned off and the participants retired to sleep. Results showed that nearly half the sleep apnea patients secreted abnormally low testosterone levels throughout the night.

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