

# Deep Vein Thrombosis in Air Travellers

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**V**enous thromboembolism (venous thrombosis and pulmonary embolism, VTE) has long been postulated as a potential complication of long distance air travel. With the increase in airlines, air routes and flights all over the world, large number of passengers are traveling long distance air travel lasting upto 18 hours. Many of them are having one or more risk factors for VTE such as old age, obesity, hypertension or previous DVT. The concern of VTE in air travel has increased manifold over the last several years, which has resulted in research on several aspects e.g. prevalence, pathophysiology of DVT in air travel, preventive measures etc. We have reviewed the relevant literature and are providing guidelines on preventive measures for VTE during air travel.

## Incidence

Venous thrombosis related to air travel was first reported in 1954 in a 54 yr old doctor, who developed DVT following 14 hour long flight (Homan 1954).<sup>1</sup> In 1977 Symington, believing that the most important cause of DVT in air travel is prolonged sitting in cramped position in long distance flights, coined the term 'economy class syndrome' (Symington 1977).<sup>2</sup>

The true incidence of DVT in air travel is unknown and it is very difficult to estimate exactly because large number of DVTs can be either silent clinically or may occur upto 30 days after air travel. Diagnosis of DVT may be clinical or by different imaging techniques with different sensitivity and specificity. Therefore, it is difficult to estimate true prevalence and determine the pathogenesis of DVT. Dimber and their colleagues were unable to show that in a workforce of over eight thousands employees of World Bank, the subset of nearly five thousand, who were frequent international business travellers had a higher incidence of DVT.<sup>3</sup> In various studies the risk of developing DVT has varied between 0.1 to 10.34 %.<sup>4,5</sup> Duration of air travel plays a major role with increasing risk of DVT

and PTE. The risk particularly increases if time of air travel is more than 6 hours. Two recent studies have shown the risk of PTE at 2.57 PTE per million passengers if flight time is >8hrs<sup>6</sup> and 4.8 PTE per million in flights of more than 12 hours.<sup>7</sup> It has been estimated that 1 in 250,000 passengers over 65 yrs of age die suddenly from pulmonary embolism during long distance flights.<sup>8</sup> Kuipers et al evaluated the risk of DVT among frequent travellers employees of large international air companies. In a total of 8,755 employees, who were exposed to long haul flight of 6,872 exposed person years (PY), incidence of thrombosis, was 3.2 /1000 PY as compared to 1.0 /1000 PY in individuals not exposed to air travel.<sup>9</sup> In same study Kuipers concluded that long distance travel increases the risk of DVT approximately 2-4 fold and the absolute risk of a symptomatic events within 8 weeks of flights longer than 4 hours is 1/4600 flights.<sup>9</sup> The House of Lords observed that for every million persons undertaking a long journey over one year, additional 200 cases of DVT will occur, which means one of 5,000 passengers making long haul flights will develop DVT.<sup>10</sup> Thoracic Society of Australia and New Zealand has cited the incidence of VTE in air travel between 4.5% and 10% using ultrasound scanning in passengers flying for longer than eight hours.<sup>11</sup> The presence of risk factors increases the risk substantially while the risk of developing VTE is negligible in healthy adult with flight duration of less than 4 hours. Another way to assess the risk of travel is to study the patients admitted to hospital with venous thromboembolism. In a study among 207 such patients, 33 had undertaken long distance flight over previous 31 days.<sup>12</sup> In 160 patients of venous thromboembolism in association with travel of more than 4 hours over previous 4 weeks, the odds ratio was 4.0 (9.5 % C.I. 1.9 to 8.4).<sup>12</sup> Asymptomatic thrombi of uncertain clinical significance are much more common and their true incidence is unknown. Over the years several risk factors have been observed (Table 1). Persons with presence of one or more risk factors are at higher risk of developing DVT or PTE. The risk is likely to increase with increasing number of risk factors in an individual.

Philbrick and colleagues in their extensive review of 25 studies (10 cohort studies, nine randomized controlled trials and six case control studies) observed VTE risk from none to 12% of travelers.<sup>13</sup> The studies performing ultrasound surveillance found much higher VTE in travelers. One of those studies using D-dimer test followed by 3 months of surveillance for symptoms of VTE reported a cumulative VTE rate of 1.8%.<sup>14</sup> Philbrick and colleagues used logistic regression model to evaluate the risk factors for development of VTE observed that mode of screening method, travel duration, presence of clinical VTE risk factors were observed as statistical significant on multivariate analysis (Table 2).<sup>13</sup>

## Pathogenesis

In 1859, Virchow postulated that there are three determinants required for venous thrombosis, popularly called as Virchow's triad. These include (1) venous stasis (2) vessel wall changes and (3) hypercoagulability. In DVT during air travel prolonged immobilization in cramped positions which ultimately leads to venous stasis seems to be the most important underlying factor.

**Table 1 : Main risk factors for venous thromboembolism**

- Older age (>60yrs)
- Obesity
- Varicose veins
- Previous DVT/VTE
- Cardiac failure
- Cancer
- Chronic medical illness
- Recent major surgery
- Recent major trauma (particularly involving lower limbs)
- Immobility of longer duration
- Women on oral contraceptive pills or hormone replacement therapy
- Previous history of thrombophilia
- Traveling in economy class

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Table 2 : Logistic regression model for VTE

Variable	Odd ratio	95% confidence interval	P value
1. Screening method			
Clinical	1.0		
Ultrasound screening	390.0	200-761	<0.0001
2. Travel duration (Hours)			
< 6	0.011	0.0019-0.11	<0.0001
6-8	1.0		
> 8	2.3	1.4-3.6	<0.0001
3. Clinical VTE risk			
Lower	1.0		
Higher	3.8	2.2-5.8	<0.0001

If the person is having any other risk factor then the additional factors also come into play. Other than immobilization many other factors have been investigated as additional pathogenetic determinants but none of them have been conclusively shown to be of significance. These include dehydration, low cabin air (oxygen) pressure or local procoagulant changes in leg vessels during prolonged sitting.

1. **Coagulation Activation:** Initially reduced cabin air pressure was postulated as a mechanism for increased risk of DVT in air travelers. Generally the cabin air pressures in long distance flights are equivalent to an altitude of 1524 to 2134 meters and maximum permissible altitude equivalent of 2,438 meter. At this level the reduced partial pressure of oxygen in inspired air results in a decrease in arterial oxygen saturation to 93% in healthy resting individuals.<sup>15</sup> Older age and associated chronic cardiac or pulmonary ailments may lead to higher drop in oxygen saturation. In an experimental study it was shown that human venous endothelial cells showed increased procoagulant activity during hypoxic conditions.<sup>16</sup> A study by Bendz et al showed an increase in TAT (thrombin-antithrombin complex), prothrombin 1+2 and factor VIIa and a decrease in factor VII antigen and tissue factor pathway inhibitor in a group of 20 healthy men exposed for 8 hours to hypobaric hypoxia which was equivalent to an altitude of 2,400 meters.<sup>17</sup> But a larger study by Toff et al in 2006 failed to show any significant changes on coagulation, fibrinolysis or endothelial function during air travel of 8 hours durations.<sup>18</sup> A recent study by Ansari et al again confirmed that even in lower links, prolonged daytime cramped sitting is not associated with significant procoagulant changes in healthy adult male volunteers. Schreijer et al<sup>19</sup> observed presence of prothrombin fragment 1 and 2, TAT and D-dimer in 4 of 63 (6.3%) volunteers after 8 hours of flight but none in the control situations. Rise in TAT was observed in 11 of 16 (17%) of individuals. Individuals with presence of V Leiden mutation and on oral contraceptives were at higher risk. These authors concluded that activations of coagulation occur after 8 hours of flight.<sup>20</sup>
2. **Dehydration:** A low moisture cabin leads to slight dehydration during air travel. A progressive rise in hemotocrit and a constant increase in plasma protein concentration and increase in plasma osmolality along with increase in urine osmolality and specific gravity have been observed. Sinam and Krol<sup>21</sup> showed that healthy persons exposed to an eight hour simulated flight at an altitude of 2438 meters with 8-10% of humidity exhibited increased mean plasma osmolality, mean urine osmolality and urinary specific gravity, all indicating the development of dehydration during air travel. However, Schreij and colleagues observed in a study on 71 volunteers that fluid loss does not contribute to thrombus formation.<sup>22</sup>

3. **Venous Flow:** It has been observed that venous flow is two-thirds lower in person in sitting posture than in supine posture. After an hour of quiet sitting progressive rise in hemotocrit along with plasma protein has been observed.
4. **Cramped Position:** Cramped position may aggravate venous stasis by compressing the veins following external compression from the seat especially among elderly persons. In the LONFLIT-3 study by Cesarone et al, 85% of DVTs occurred in passengers on non-aisle seats suggesting a potential role of decreased leg mobility due to cramped position.<sup>23</sup>

Thus it has been postulated that combination of factors such as (a) dehydration with a sluggish venous blood flow during prolonged sitting in cramped position (economy class) (b) prolonged immobilization, (c) in presence of risk factors and (d) activation of coagulation system in some contribute for VTE during prolonged air travel of over 8 hours duration.

## Incidence of Concern

Number of persons traveling long distances via air is increasing continuously. According to International Civil Association approximately 2 billion people traveled in 2005 by air. Frequency and capacity for low cost sector have shown rising trend over the last few years. A growth of 13% was observed in July 2008 vs July 2007. Over the years more passengers are preferring to travel long distances. Many of these passengers harbor risk factors for DVT. Even a small percentage of increased risk in this large number of passengers will lead to substantial increase in cases of DVT.

Despite all research going on, we still lack data which could identify the risk involved to a person traveling by air. The presence of risk factors carries higher risk of thrombosis. If we can identify these people and can apply some preventive measure then definitely we can prevent a large number of DVTs.

## Prevention

Various preventive measures for prevention of VTE have been used. Methods used in prevention can be either non-pharmacological or pharmacological while the effectiveness of these measures in prevention of VTE needs to be determined. It is still not clear who should take which measure. The various preventive measures along with their pros and cons are given below:

1. **Physical Therapy:** Frequent change of posture has been advised traditionally to anyone during flights along with avoidance of postures which might block the circulation. Though this is useful during long flights, it is not of any benefit in short duration flights. Exercises such as dorsiflexion of foot and occasional walk in the cabin to prevent the sluggish blood flow has also been recommended. The avoidance of tea and coffee has also been recommended by some as they may lead to possible dehydration due to their diuretic action. Frequent intake of liquids has also been recommended with same logic with uncertain benefit.
2. **Compression Stockings:** These stockings exert gradually increasing pressure downwards, thigh to ankle. This along with limbs activity is thought to increase blood flow in deep veins of leg by diverting blood from superficial to deep vein. The increased blood flow reduces venous stasis and decreases the blood clotting and prevents the thrombosis. In a recent Metaanalysis Clarke et al showed

that there is significant decrease in incidence of DVT by wearing compression stockings. However, they could not show that the decrease in the incidence of DVT translates into prevention of pulmonary embolism or symptomatic DVT.<sup>24</sup> In studies analyzed there were 2,637 participants and a total of 50 DVTs, all of them were asymptomatic. Out of these 50, 47 were in the group which didn't use compression stockings and only 3 events in group that used the stockings (P<0.00001). Uses of compressing stockings can decrease the incidence by approximately 20% (1-3 /1000 persons) along with a significant reduction in leg edema.

3. Aspirin: There is no consensus on the use of aspirin in DVT prophylaxis during air travel. Though its use is widely recommended. In DVTs, in other circumstances aspirin has only a modest benefit to prevent venous thrombosis. Thoracic Society of Australia and New Zealand have recommended the use of Aspirin to person with mild to moderate risk on the basis of effect on prevention of PTE.<sup>11</sup> However, the role of aspirin for DVT in legs is uncertain.
4. Anticoagulant: Role of anticoagulants in prevention of DVT is uncertain. As such air travel carries little risk of DVT and there is small but definitive risk of bleeding in patients on anticoagulants. But there is definitive evidence that anticoagulant reduces incidence of VTEs in patients who are at high risk of VTE. There is very little data on the use of warfarin and unfractionated heparin in prophylaxis of DVT in air traveler. Role of LMWH has been evaluated and its use decreased the incidence of VTE. LMWH is usually recommended when either the compression stockings cannot be used or with compression stockings in patient at higher risk. The schedule usually used is a single injection of daltaparin 5000 IU or enoxparin 40 U 2 hour before scheduled departure.<sup>25</sup> Its use has been left to physician's judgement based upon the individual's condition and presence of various risk factors. It is generally recommended to persons who had previous episode of DVT and have presence of risk factors.

## Conclusion

In view of increasing air passenger traffic the concerns regarding DVT in air traveler has increased over the last several years. In spite of large studies and metaanalyses there are several controversies. We still don't know the exact pathophysiology of the increased risk during and after air travel and we still lack the exact estimate of how much risk of DVT travelers have. Venous stasis, cramped position, prolonged immobilization and long flight hours have definitively been shown to increase the risk of DVT. On the other hand, a normal healthy adult male does not carry any increased risk in short duration flights. Increased risk of DVT is associated with high risk of PTE which may be fatal. In the absence of any risk factors and in short flights there is no specific intervention required. In these individuals even in long flights of over 8 hours, frequent change of posture in between and avoidance of dehydration along with walking in the cabin are adequate. Person with mild to moderate risk (1-2 risk factors), or previous history of DVT, use of compression stocking is generally recommended along with the preventive measures. Use of LMWH at present should be on physician judgment on individual basis and presence of various risk factors.

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