



Relation between Air Travel and Venous Thromboembolism

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Introduction

It has been, and still remains, a controversy whether air travel increases the risk of developing venous thromboembolism (VTE) or not⁽³⁸⁾. Sixty years ago, Homans⁽³³⁾ reported the first VTE cases related to travel. He emphasized previous where prolonged sitting was the only possible link to VTE⁽⁷⁷⁾. “Economy class syndrome” was first mentioned in the medical literature in 1977⁽⁸¹⁾. Since then, numerous articles have been published about the association between air travel and the development of VTE. Differing opinions, ideas, and conclusions illustrate how much this area of research continues to be debated.

What is venous thromboembolism or VTE? VTE is a condition that entails deep vein thrombosis (DVT) and/or pulmonary embolism (PE)⁽¹⁾. VTE affects both hospitalized and non-hospitalized patients⁽⁹⁾. VTE is newly diagnosed in 0.1% of the US and other developed countries each year^(17,88). Up to one third of these patients die within a month of the diagnosis⁽¹⁰⁾. The disease is believed to be the third major cause of hospital-related death, and the only major cause of death that may be prevented⁽³⁾.

VTE risk factors include; age, obesity, previous history of VTE, major surgery, malignancy, oral contraceptives, immobility, thrombophilia, and

trauma⁽⁶³⁾. In this paper, a discussion on whether air travel increases the risk of developing VTE will be conducted. This will involve a comparison of the condition among patients using air travel with those using other modes of transportation, including road and rail. The discussion will also focus on the possible triggering factors that may lead to this condition as a result of air transport. This involves the analysis of the environment in air travel, including cramped seating, hypobaric hypoxia, as well as dehydration. Additionally, it will compare similar situation that involve the same factors in environments other than the airplane.

Methods

A literature review was conducted utilizing Medline database (via PubMed). Dunbar Library and its staff at Wright State University assisted in this process. PubMed was accessed through the University website, and related electronic articles were downloaded. Some articles that were not available electronically were accessed and reviewed in print form. Inter-library loan service was also utilized to acquire additional reference sources.

The review involved all published literature pertaining to the risk factors of VTE, and how air

transport is related to this condition. Some of the search terms used included “*venous thromboembolism*,” “*deep vein thrombosis*,” “*pulmonary embolism*,” “*economy class syndrome*,” “*traveler’s thrombosis*,” “*risk factor*,” “*travel*.” The references of my search results were also queried. Inclusion criteria included any article that was published in the English language and was a human study. Other inclusion criteria were all published articles related to the risk of developing VTE as a result of travel. They also included any published study on simulating an aircraft cabin environment. Other articles were also added to the review to compare developing VTE as a result of similar triggering factors that are not related to travel. The current area of interest is finding the absolute risk of air travel-related VTE, excluding any article which discussed only prophylaxis and preventive measures. Finally, 46 articles were chosen to be this area of study and analysis. They include case reports, case-control studies, cohort studies, systematic reviews, and clinical trials. More studies were added to the discussion to compare different results. Other articles were also used to provide additional facts and historical context. Having done all this, a justifiable conclusion will be made on whether or not air travel increases the risk of developing VTE.

Results

This section summarizes supportive data relating travel with VTE. There is sufficient evidence that long distance travel is a risk factor to the occurrence of VTE ⁽²⁹⁾. However, this data does not confine VTE to be exclusively a result of air travel. It is reported that VTE risk increases with the duration of travel ⁽²⁹⁾. Nonetheless, severe cases of pulmonary embolism are rare ^(54,87).

The risk factors associated with air travel have raised great concern among researchers. In the several studies that have been conducted on the predisposing factors to VTE, air travel has been among the most prevalent factors ⁽⁷⁾. The risks of DVT are enhanced by the prevailing conditions

during a flight, as well as the preexisting risk factors ⁽²⁵⁾. Factors that may be associated with an increased risk in developing VTE include the duration of the flight, and other conditions that could predispose to hypercoagul ability and venous stasis in the lower limbs ⁽⁵⁹⁾. Conditions that have been cited to increase risk of acquiring VTE are individual-based, including: obesity, the use of oral contraceptives, inherited factors, and previous history of VTE ⁽⁸⁵⁾.

According to the results of 2 randomized trials ^(13,75), an incidence of between 4.5% and 10% asymptomatic DVT was detected using ultrasound scanning in passengers who flew for more than 8 hours. In another study conducted for three years at Heathrow Airport, it was estimated that 11 out of 61 sudden death cases resulted from PE ⁽⁶⁶⁾. In the survey of 182 cases of PE, eight were reported to have resulted from prolonged travel ⁽⁸¹⁾. Assessment of VTE risk is done through the evaluation of patients admitted to hospitals with this condition. Among the patients assessed, 50% of travelers were found to have engaged in air travel in the past month ⁽⁵³⁾. In 60 patients with history of air travel, half of them had no other predisposing risk factors ⁽³⁵⁾. Likewise, 45 out of 62 patients, from another study, had traveled by airplane ⁽⁵⁰⁾. However, these estimates could be far from the actual number of incidences resulting from air travel, especially based on the fact that the majority of these cases are experienced long after the flight. To confound the issue, an autopsy study showed that up to 36% of fatal PE cases occurred before boarding the airplane ⁽²¹⁾.

According to a systematic review conducted by Adi & colleagues ⁽²⁾, prolonged travel is a weak risk factor leading to incidences of thromboembolism. In a cohort study of 8,755 employees of an international organization, it was reported that the incidence of VTE after a flight of 4 or more hours was one in every 4656 passengers ⁽⁴⁵⁾. Severe cases of PE immediately after a flight are rare, especially in flights taking less than eight hours ⁽⁴⁵⁾. In flights lasting more than twelve-hours, the rate is estimated at five per million ⁽⁴⁶⁾.

Notable in this study is the fact that; not all cases of PE occur as a result of travel. If the condition has to be associated with travel, it must have occurred up to eight weeks after the travel ⁽⁴⁶⁾.

In eleven case controlled studies, it has been reported that the risk of VTE cases related to travel is more evident in individuals with pre-existing risk factors ^(6,19,24,26,34,44,51,57,58,64,82). In most of these studies, traveling for at least three hours was associated with increased risk of thrombosis. However, in two studies, the development of VTE was only observed with travel durations of between 10 to 15 hours ^(57,82). The risk after air travel was estimated to be 2 times higher among passengers with no other risk factors ^(19,51). However, the majority of the cases of VTE only occurred among patients with preexisting risk factors. The risk was up to 15 times higher in passengers known to have inherited thrombophilia and/or have been on oral contraceptives ^(19,34,51). Nonetheless, the number of those who had not had a flight but had prolonged road or rail travel was higher; 77% of the cases ⁽²⁶⁾. In fact, the majority of these case controlled studies have found no link between travel, in general, and the development of VTE ^(6,24,34,44,57,58,64,82). A descriptive study on the rate of occurrence of fatal PE estimated the rate at 0.5 per million and 1.3 per million occurring among travelers taking flights of more than 3 hours and more than 8 hours, respectively ⁽⁵⁸⁾. The time frame that was reported for development VTE after prolonged flight was estimated at between 2 and 8 weeks ⁽⁴⁰⁾.

In four prospective studies conducted on the development of VTE following travel, objective methods of evaluation of VTE were used prior to and after traveling ^(36,37,73,74). In all these studies, the duration of travel was more than 8 hours. Four cases of PE and five cases of DVT, a total of 9 VTE cases, were diagnosed after evaluating 878 passengers⁽³⁶⁾. Also, 7 cases out of 964 passengers were diagnosed with DVT ⁽⁷⁴⁾. On the other hand, and in two different studies, no one was diagnosed with VTE after evaluating 1059 passengers ^(37,73).

Generally, a combination of the studies revealed that the development of VTE was estimated at 16 out of 2,901 cases, which translates to 0.5%.

In three retrospective studies, the association between long-distance flying and the onset of PE was evaluated ^(43,49,60). The studies included data on more than 180 million passengers. In these studies, it was realized that early onset of VTE was rare with one in every 115 million travelers flying for less than 6 hours being reported to be at risk. The surveys reported sufficient evidence for the association of the early onset of VTE with long-distance travelling. Among the major study ⁽⁴⁹⁾, the rate of early occurrence of PE was estimated at about 5 per million; that is for flights of more than 12 hours. PE was reported among individuals who had a prolonged travel, with more than 93% of the individuals having traveled for more than 8 hours. Likewise, the majority of the patients that developed VTE had pre-existing risk factors for this condition.

VTE was linked to prolonged train travel in two different case reports ^(39,55). And the term "*Rail Coach Syndrome*" was proposed ⁽⁵⁵⁾. Another case report, on a 40 year-old male who developed PE after watching 3 consecutive American football games, proposed the term "*Bowl-game pulmonary embolism*" ⁽⁸⁶⁾. Two studies have examined the relation between jobs of prolonged sitting, in non-travel situations, and VTE ^(30,80). Both of them have concluded that prolonged sitting is a risk factor for developing VTE. Also, a case report proposed the term "*e Thrombosis*" after prolonged sitting in front of a computer ⁽¹²⁾. With regard to studies on specific triggering factors in the airplane environment, hypobaric hypoxia was first evaluated in 2000 ⁽¹⁴⁾. The study was performed in a hypobaric chamber simulating the airplane environment. It concluded that hypobaric hypoxia activates coagulation and may predispose to VTE after flight. In addition, another study supported that conclusion after exposing volunteers to; eight hours of real air time, eight hours of sitting in a movie theatre, and eight hours of normal daily life ⁽⁷²⁾. On the other

side of the controversy, and in the majority of hypoxia studies, it was found that hypobaric hypoxia does not activate coagulation system^(15,23,32,69,79,83). In fact, two of these studies concluded that prolonged sitting would decrease thrombin generation, and should counteract the effect of venous stasis that might result from immobility^(15,79). Although there is a fluid shift to the legs after prolonged sitting, this will not affect deep veins' diameter nor will it increase the risk of developing VTE⁽⁵⁶⁾.

Dehydration, secondary to alcohol consumption or low humidity, was believed to be one of the triggering factors⁽⁷⁰⁾. Walking to and from the bathroom, as a result of alcohol consumption, would counteract any risk of developing VTE secondary to dehydration⁽⁶⁵⁾. Dehydration resulted after a study, in a low humidity and high altitude environment, on 6 healthy people⁽⁷⁶⁾. On the other hand, Landgraf and colleagues⁽⁴⁸⁾ found changes to be within normal physiological limits, and are not enough to cause VTE in healthy individuals. Likewise, no association was found between dehydration and developing VTE, at all⁽⁷¹⁾.

Discussion

The outcomes of the studies conducted in the results section of this paper can demonstrate that there is an association between long-distance traveling and the occurrence of VTE. With increasing numbers among air travelers, VTE will continue to occur and raise the question about the absolute risk^(22,28). A number of factors have been proposed to relate this condition with prolonged traveling. However, not only can VTE develop after air travel, but could also occur after other modes of traveling, provided that the duration of travel is prolonged⁽⁴⁾. The risk factors of VTE, apart from old age, include but are not limited to; surgery, trauma, immobility, previous history of VTE, cancer, obesity, hormonal therapy, as well as thrombophilia⁽⁵⁾.

Among the individuals analyzed in the results earlier presented, some related the occurrence of VTE to the use of oral contraceptives, with

increased risks among long-distance travelers as compared to the non-travelers. Oral contraceptives have been classified as one of the factors that predispose women to VTE during or after prolonged flights⁽⁵¹⁾. This leads to the questioning of why this happens and why the risk factor is augmented in such a case.

Moderate and high risk factors linked with VTE were also discussed. This is during or soon after the flight. It was also noted that VTE is associated with high-risk factors, including previous history of VTE, obesity, and cancer. However, majority of the cases of VTE only occur among patients with preexisting risk factors. The factors are similar to the increased risk of VTE resulting from surgery or prolonged immobility, even among hospitalized patients. It is, therefore, worth noting that the flight-related VTE is, in one way or the other, similar to VTE resulting from other instances, including prolonged rail and car transport. If a person is at high risk of VTE on the ground, the risk will also be high in long-haul flights⁽³¹⁾. Among high risk travelers, individuals who have a past medical history of VTE will have an increased risk in other circumstances, other than air transport. Although screening can help in the assessment of thrombotic cases, it is less significant in predicting the increase of risk factors during a long-haul flight among healthy individuals.

The studies discussed above have examined the relationship between travel, especially air travel, and VTE. Nonetheless, the studies employed varying methods of data collection, which led to varying data analysis. In all these cases, the asymptomatic cases of VTE were estimated at 5 to 20 times more than the symptomatic cases. In the data collected, long-distance travel ranged in duration from three to ten hours, with some cases considered lasting more than 12 hours of travel. Similarly, the duration between travel and appearance of symptoms associated with VTE ranged from a few hours to 8 weeks. Among the studies analyzed, some of them reported that prolonged travel may lead to increased risk of

VTE. None the less, the majority of the studies did not report any significant evidence relating travel with VTE. Furthermore, the majority of the studies found air travel to be a weaker risk factor of VTE.

The results from the analysis of various literatures can clearly demonstrate that long distance air travel increases the risk of VTE three times more than the normal risk factor⁽²⁰⁾. However, not only is the risk of VTE increased by air travel, but also by other modes of transport. Car, bus, and train transport are also predisposing risk factors to this condition⁽⁸⁴⁾. What this implies is that the increased risk of VTE is mainly attributed to protracted restricted mobility, rather than the environment within the cabin of an airplane. The risk ends to be the same in all modes of travel and only depends on the duration of travel, as well as previous risk factors depending on the individual. Similarly, the risk of developing VTE decreases with increased time after travel, with majority of the air travel related cases occurring in the duration of one to two weeks after the flight⁽⁶²⁾.

As was previously mentioned, the majority of the travel related VTE occur among passengers with preexisting risk factors. This accounts for 75 to 99% of individuals who develop the condition^(27,41,42,52,61). In people with no previous risk factors, the risk of VTE was found to be very low⁽⁸⁾. While a combination of travel with previous history of VTE in an individual may influence the risk^(18,47).

Although Bendz and colleagues⁽¹⁴⁾ found hypobaric hypoxia to be an important factor in activating the coagulation system, their study did not have a control group and the coagulation markers were abnormally high at the baseline. It is worth noting that changes of some biochemical markers were exactly the same among air and bus travelers^(67,68). Likewise, stress might be responsible for the activation of some coagulation markers, but hypoxia does not have a direct effect⁽¹⁶⁾. Similarly, the discussion presented in this paper did not find any justifiable association between dehydration and travel related VTE. However,

sufficient data can be relied on in justifying the fact that only prolonged immobility increases the risk of VTE. Therefore, this disregards the mode of travel that is being used. In all the modes of travel, including road and rail transport, prolonged durations of travel increase risks of VTE.

Linking VTE and/or an activated coagulation system to car, bus, and train travel raises the question on the accuracy of the term "*economy class syndrome*." Likewise, VTE cases and activation of coagulation system was equal among business and economy class passengers⁽³⁷⁾. This also eliminates any association between cramped seating and the development of VTE.

The reason why air transport is usually linked to VTE is that during air travel, travelers rarely take a break. This leads to prolonged durations of sitting with less mobility. As was previously discussed, immobility is among the major factors that raise the risk. In other modes of travel, including car, bus, and train, travelers usually take a break, enabling them to relax, thus, reducing the risk of developing VTE. However, the risk after air travel may not be more or less as compared to ground transport. This is mainly because the risk is more dependent on the prolonged sitting.

"*Seated Immobility Thromboembolism*" (SIT) was first proposed in 2003⁽¹¹⁾. Although it is a proper term, it is more frequent in high risk individuals, as well⁽⁷⁸⁾. SIT may be a more accurate term for VTE related to travel and/or prolonged sitting. Studies have covered multiple and single triggering factors in the airplane environment, and most of the conclusions are rejecting the hypothesis that air travel in and of itself is a risk factor. Debate might continue with every new diagnosis of VTE after air travel, but prolonged sitting will be the only major risk factor in low risk passengers. In fact, this was described more than seventy years ago when Dr. Simpson reported the first cases of VTE after prolonged sitting in air-raid shelters in London during World War II⁽⁷⁷⁾.

Conclusion

Venous thromboembolism is a condition that is associated with reduced mobility. It, therefore, occurs among individuals with restricted movements, especially among hospitalized patients, travelers, and workers seated for extended periods of time. However, some researchers have alleged air travel to increase the risk of developing this condition, as compared to other modes of transport. Nonetheless, studies have stated that the risk of VTE among travelers entirely depends on the duration of travel. In this regard, air travel may not lead to increased risk as compared to other modes of transport.

As the discussion in this paper has summarized, not only does prolonged immobility increase the risk of VTE, but other predisposing factors do as well. An individual may be more at risk based on hereditary thrombophilia, while others may be obese, had recent surgery or had a previous history of VTE. Similarly, this paper has reported that, although prolonged travel increases the risk of VTE, the risk decreases gradually with increased duration after the travel. However, the earlier symptoms of VTE may appear long after travel has concluded, to duration of up to 8 weeks. What this implies is that, despite the association of some cases of VTE with travel, others are not travel-associated. Also, symptoms do not definitively ascertain when thrombus was generated; before, during, or after the journey.

As the discussion in this paper has put forward, the risk of VTE only increases with the duration of travel, and is not dependent on the mode of travel. What this implies is the fact that VTE also appears as a result of prolonged car and train transport, when the other predisposing factors are kept constant. In this regard, it is worth concluding that air travel does not promote the risk of VTE more than other modes of traveling. The major factor that increases the risk is the duration of prolonged sitting. Therefore, no matter what was the event preceding the diagnosis of VTE after prolonged sitting, SIT is a more appropriate term.

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