

Medical Hypotheses

Is there a connection between long airplane flight, venous thromboembolism, and sleep-disordered breathing?

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Abstract

Commercial passenger flights have been increasing around the world. The effect of these flights on health is unclear. Venous thromboembolism has been noted after recent long-distance airplane flight, even in the absence of other risk factors. Hypoxia caused by the low ambient pressure during flights could contribute, and individuals with obstructive sleep apnea may be particularly vulnerable. The association between the effects of long airplane travel and sleep-disordered breathing deserves further study.

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1. Introduction

Commercial passenger flights have been increasing around the world in recent decades; approximately two billion people now travel each year [1,2]. The effect of these flights on health is unclear. An association between prolonged sitting and venous thromboembolism (VTE) was first recognized during the Second World War, with reports of fatal pulmonary embolism (PE) in people who slept at desk chairs. The frequency of VTE and PE overall is controversial; reported prevalence ranges from 1% to 10%, and retrospective clinical series suggest that up to 20% of patients presenting with thromboembolism have undertaken recent air travel [3]. Long-distance air travel has been associated with a high risk of pulmonary embolism which can be fatal [4]. Nevertheless, the pre-existing risk factors for VTE are still

unclear. Preliminary data suggest that obstructive sleep apnea syndrome (OSAS) may increase risk for VTE independently of the severity of the disease [5,6]. However, the preliminary data published in the two letters to the editor just referenced have not been replicated or confirmed in full-length peer-reviewed reports to our knowledge.

Hypoxia induced by low ambient oxygen levels in airplane cabins can be associated with changes in platelets [7]. Platelet number or function may be altered in circumstances (high altitude) that may also induce hemostasis [8]. It is well recognized that altered platelet aggregation is one of the strongest risks for venous thromboembolism. Hypoxia-induced platelet activation and aggregation may be due to increased circulating catecholamine levels but it is not known whether hypoxia can affect platelets directly [9]. Hypoxic conditions during flight also could cause changes in many other domains of health, biological function, and quality of life. The transport of oxygen to tissues for physiological functions depends on the presence of oxygen in the

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environment, mechanisms of breathing, distribution via the blood stream, and in the end, oxygen consumption.

Long flights may be a particularly important risk factor for VTE. Kraaijenhagen et al. [10] found that long traveling time is a strong risk factor for VTE, whereas journeys lasting less than 5 h showed no association. However, available data raise the possibility of important confounders such as age, previous episodes of venous thrombosis, malignant disease, surgery, and immobilization. Diagnoses may commonly be missed when VTE creates no symptom. Less than half of patients with VTE develop symptoms, and only a few of those go on to have clinically detectable PE. The relationship between pulmonary embolism and VTE still awaits further clarification. Scurr et al. [11] studied passengers over 50 years of age without risk factors for VTE using duplex ultrasonography. They found symptomless VTE of the calf in 10% within 48 h after long flights. Schreijer et al. [12] suggested that airplane flight can cause hypoxia and thereby increase risk for VTE. These authors showed enhanced activation of coagulation pathways after flights in comparison to two control exposures. Their findings suggest that hypoxic and hypobaric conditions associated with airline flight increase thrombin generation, especially in individuals with risk factors for thrombosis.

The strong impact of OSAS on public health is reflected, in part, by the substantial size of estimated costs to society [13]. There are coagulation abnormalities in patients with OSAS, but the mechanisms are unclear. Preliminary data suggest increased platelet activation in OSAS, most likely promoted by recurrent episodes of hypoxemia [14]. Parasympathetic and sympathetic tone change in all subtypes of sleep-disordered breathing (SDB). Circulating catecholamine levels increase with sympathetic activation [15] and could affect platelets. We wonder whether activated coagulation pathways could possibly be identified and addressed prior to long-distance flight as a strategy to reduce risk for VTE. Could patients with SDB have particular vulnerability to changes in coagulation pathways before, during, and after their travels? If so, could preventative strategies be targeted to these individuals? What connection can we make among SDB, airplane travel, and factors that promote VTE?

2. Hypothesis

We suggest that patients with SDB may be more vulnerable than other passengers to develop VTE during long flights. This hypothesis has received scant prior consideration, and the aim of this article is to advance the idea, and by inference, the notion that preventative effort may be warranted to protect passengers on long flights who have SDB.

3. Testing the hypothesis

Direct testing of our hypothesis would require prospective investigation, before and after long flights, in a sample of passengers with and without well-defined SDB. Ages, health status, country of origin, and other factors would need to be carefully controlled.

4. Implications

We hypothesize that in patients with SDB, the consequences of the hypoxic and hypobaric changes associated with flight may be augmented. The hypoxia caused by the low ambient pressure of aircraft cabins in patients with SDB may increase risk for venous thromboembolism by early-onset thrombocytosis associated with changes in the release, activation and aggregation of platelets.

Obstructive sleep apnea, the prototypical form of SDB, generates repeated cessation of breathing and marked associated increases in muscle sympathetic activity, which remains elevated throughout both night and day in patients with chronic untreated OSAS. Associations between OSAS and cardiovascular disease, including arterial hypertension, stroke, and heart disease, have been well described [16]. Patients with OSAS may well have increased risk for VTE [5,6]. However, available data do not clarify whether such risk would stem from obstructive respiratory events during sleep or associated confounders, such as obesity and hypertension conditions that have been associated with hypercoagulation state [17]. The mechanisms in patients with OSAS that activate the coagulation system are likely to involve sympathetic overactivity, selective activation of inflammatory molecular pathways, endothelial dysfunction, abnormalities in the process of coagulation, and metabolic dysregulation [17,18]. Our hypothesis is that this state of hypercoagulation in patients with OSA may be exacerbated during long travel flights. Bendz and colleagues [19] investigated effects of acute exposure to reduced air pressure, similar to that encountered in airplane cabins. Concentrations of prothrombin fragments 1 and 2, levels of thrombin–antithrombin complex, and activity of factor VIIa all increased. These results suggest that rapid exposure to air pressure encountered in airplane cabins activates coagulation. This activation is likely to be clinically relevant and may contribute to the increased risk of VTE. Activation of coagulation coincided with increased factor VIIa activity, suggesting activation of the tissue-factor pathway of coagulation.

OSA is associated with increased erythrocyte aggregation and adhesion [20]. Evidence suggests that even mild SDB is associated with changes in inflammatory markers, such as an increase in IFN-gamma and IL-8 levels [20], and also plasma adhesion molecules [21].

However, measures of inflammatory status do not correlate well with sleep fragmentation indexes [20]. Patients with SDB showed plasma elevations of P-selectin, a good marker of platelet activation that correlates with respiratory arousals [21], but the contributory role of arousals in this process is still unclear. Inflammatory processes are likely to be consequential, however, and may contribute for example to cardiovascular morbidity [22]. We hypothesize that activation of coagulation pathways could be associated with activation of inflammatory molecular pathways. After long airplane travel, the inflammatory status of patients with SDB might differ from that of patients without SDB, and it can increase the risk for VTE after long travel.

Philbrick et al. [23] found that there is a risk of symptomatic VTE from prolonged air travel, and if the VTE rates were identified through usual clinical care, the risk could be as low as 27 cases per million travelers. This estimate is equivalent to only 1.1 VTE per million person-days, and is perhaps so low because of a healthy traveler effect. This estimate is less than the baseline risk reported in general populations, estimated to be 1.9–5.2 VTE per million person-days [23]. It is possible that most asymptomatic thrombi can resolve without treatment but that some cases progress to symptomatic VTE during the several weeks after travel. Philbrick et al. [23] also showed that VTE risk is very low when flight time is less than 6 h, but is progressively greater with longer-duration flights. The overall VTE risk with air travel is much higher than that reported for “low-risk” surgical patients, persons on bed rest for more than three days, increasing age, laparoscopic surgery, obesity, pregnancy, and varicose veins [24]. The reported risk with air travel is similar to that reported for “moderate” risk factors such as arthroscopic knee surgery, congestive heart failure, hormone replacement therapy, stroke, postpartum pregnancy, and previous thromboembolism [25,26].

Finally, in our opinion the effects of long travel in patients with SDB are also likely to be associated with autonomic changes. Acute exposure to hypoxia can be associated with changes in sympathetic activity [27,28]. The hypoxia exposure of patients with OSA during long-distance plane travel may exacerbate chronic sympathetic activation. Furthermore, heart rate modulation is more related to parasympathetic activity than sympathetic activity in patients with mild SDB [29]. In these patients, the lifting of the parasympathetic modulation at the end of an episode of high-resistance breathing could be an important contributor to heart rate changes and could play a more important role for the cardiovascular mortality than sympathetic chronic stimulation [30]. In short, patients with SDB are likely to have chronic autonomic changes before their long-distance air travels that combine with in-flight hypobaric and hypoxic conditions to greatly increase risk of VTE.

We suggest that several additional types of studies are warranted. One approach would be to compare patients with and without SDB while controlling for age, gender, body mass index (BMI), history of known VTE, and other recognized VTE risk factors. Both groups would be evaluated before and after long plane flights to assess for VTE. A second approach would be to assess whether patients with VTE after long plane flights are more likely than appropriately-matched passengers (on the same flights) without VTE to have SDB. If prolonged airline flight does increase risk of VTE disproportionately in patients with SDB, prospective interventions such as in-flight exercise, ambulation protocols, or pre-flight prophylactic anticoagulation may prove worthwhile. Further studies should be done to confirm and quantify the magnitude of risk in those affected by SDB and to investigate potential prophylactic measures. However, in the meantime, we believe that sufficient evidence exists to merit warning patients with untreated SDB that they may be at increased risk for VTE during long flights.

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