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DEBATE

Interventions to prevent venous thrombosis after air travel, are they necessary? Yes

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Over 300 million passengers travel yearly on long-distance flights in cramped positions. While the association between air travel and venous thromboembolism (VTE) has been recognized for over 50 years [1], a growing number of reports over the past 7 years shed light on the epidemiological and pathophysiological aspects of travel-related thrombosis, emphasizing the question of prophylaxis in this setting.

The scale of the problem

Reports on passengers with severe pulmonary embolism (PE) following long-haul flights, diagnosed on arrival at major airports, suggest that while the risk increases exponentially with flight duration, the actual incidence is very low [2,3]. However, this is an underestimation of the problem as it is now well established that VTE can develop up to 1 month after a long-haul flight, with a particularly increased risk during the first 1–2 weeks after travel [4].

It is estimated that 5–15% of all diagnosed VTEs are associated with long-haul flights, with a higher incidence not surprisingly observed in remote geographical locations [5,6]. The incidence of symptomless VTE following long-haul flights (> 8 h) has been estimated by a number of studies using Doppler sonography and CT angiograms. The incidence of sonographically documented deep-vein thrombosis (DVT) ranges between 2% and 10% [7–9] within 48 h of landing, which is comparable with the rate of sonographically documented DVT observed in the group of acutely ill medical patients without prophylaxis in the PREVENT trial [10]. A recent study from New Zealand found an eightfold increase in fatal PE in those who had traveled by air for longer than 8 h [11].

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Mechanism of thrombosis

Elucidation of pathophysiological mechanisms of thrombosis during air travel is of importance in terms of defining risk and utilizing potential prophylactic interventions [12]. Thrombosis developing after prolonged sitting in cramped positions in shelters was described long ago [13], and this pathology may be also observed in other situations of prolonged sitting during travel by trains and motor vehicles [14]. Restriction of the activity of natural venous pumps in the cramped sitting position may increase the risk for VTE [15].

VTE more frequently affects non-aisles passengers, emphasizing once again the role of prolonged sitting during long-haul flights. Lack of passengers' awareness of the danger contributes to the potential devastating outcome. Dehydration is common, due to cabin microclimate conditions, lack of sufficient water intake and increased alcohol consumption.

It has been suggested that cabin pressure, which is equivalent to hypobaric conditions at 1800–2400 meters altitude, leads to hypoxia and coagulation activation [16]. However, another study in a hypobaric chamber failed to support the hypothesis that hypobaric hypoxia is associated with prothrombotic alterations in healthy individuals at low risk for VTE [17]. Furthermore, a study in healthy volunteers did not demonstrate hemostastic changes during a normobaric hypoxia [18]. A recent study in young adult volunteers demonstrated that thrombin–antithrombin complexes increased by 30% in travelers after 8 h flight, supporting the concept that, indeed, too much clotting occurs during air travel, with the highest elevation demonstrated in thrombophilic women on oral contraceptives [19]. However, long-haul flights do not activate hemostasis in young healthy men [20].

Thus, the mechanistic question regarding too much sitting or too much clotting during air travel is still open. Meanwhile, the increased thrombotic risk necessitates prophylactic measures.

Risk assessment

It is now well established that inherited and acquired factors increase the risk for travel-related thrombosis. This risk is

particularly high in long-haul travelers aged over 40 years with co-morbid conditions such as cancer, congestive heart failure, recent surgery or previous VTE or stroke [4]. The risk is also elevated in passengers with varicose veins, obesity or recent trauma. Patients with thrombophilia, pregnant women or women on oral contraceptives or hormone replacement therapy are also at an increased risk [9,21].

A recent Australian study demonstrated that one risk factor was found in 84% and two risk factors in 52% of passengers who developed travel-related thrombosis [22]. Recent surgery before air travel is a risk factor and surgery shortly after a long-haul flight could be a prescription for VTE [23]. As more patients are traveling long-distance for surgical procedures [24], this issue needs further investigation.

While assessment of thrombophilic risk factors can help in identifying those at risk, it should be noted that even passengers with low to moderate risk can develop travel-related thrombosis. In fact, in the study by Lapostolle *et al.* [6], over 90% of the patients who developed PE were only at a moderate risk (age over 40 years, varicose veins or hormonal therapy), and the NZATT study demonstrated an incidence of 1% VTE that necessitated anticoagulation in passengers with low to moderate risk [25]. This can be explained by too much flying, as the VTE risk increases exponentially with flight duration. Indeed, one long-haul flight increases the annual risk of VTE by 12% [4]. The risk is further augmented following consecutive long-haul flights and potentially following a number of adjacent shorter flights. Lags of more than 8 and 12 h are associated with a respective fourfold and eightfold increase in VTE risk. It is expected that passengers traveling 17 h non-stop by Airbus 380 and Boeing 787 will be at an even higher risk for thrombosis. This issue appears to be of much importance and thus requires special attention.

We have currently constructed a thrombosis risk assessment model for air passengers. This model uses a score for each risk factor and the total score differentiates between low-, intermediate- and high-risk groups, enabling stratification for specific interventions.

Preventive measures

It has been advocated that passengers should be alert to the potential risks of air travel and need to be encouraged and guided to exercise regularly, perform short walks in the aisle and avoid dehydration and excessive alcohol intake. The effect of flight-related behavior on risk for venous thrombosis was evaluated in a recent study [26]. While excessive alcohol intake increased the VTE risk, ample non-alcoholic fluid intake did not reduce the thrombotic risk. It has also been shown that mild leg exercise can prevent stasis but has no influence on hemostasis [27].

In general, active prophylaxis includes physical measures and antithrombotic drugs. If indeed prolonged immobilization is the main risk factor, elastic stockings should be advised. This has proved to be beneficial in patients with standard risk, by reducing the rate of DVT from 12% to 0% in the study by Scurr *et al.* [7] and from 5% to 0.24% in the LONFLIT investigators' study [28]. In addition, stockings can alleviate edema, which is common after long-haul flights [29]. A recent Cochrane review evaluated available randomized trials on prevention of symptomless travel-related thrombosis with elastic stockings [30]. Significant risk reduction of symptomless DVT has been observed in the elastic stockings group. However, seven of the nine trials included low- or medium-risk passengers and only two included high-risk travelers.

The role of a variety of mechanical devices that can prevent stasis and increase circulation is currently under investigation in this setting. The Dutch group evaluated the effect of an innovative intermittent mechanical calf compression device designed for prevention of travelers' thrombosis in normal volunteers [31]. The results showed that the device increased venous blood flow but did not affect significantly thrombin generation and fibrinolytic parameters.

Antithrombotic prophylaxis has been evaluated in limited small-scale studies. Of note, in the NZATT study, 17% of participants wore elastic stockings and 31% took aspirin. However, despite these measures, several individuals developed VTE [25].

The LONFLIT III study demonstrated in high-risk long-haul flight passengers that while aspirin at a dose of 400 mg given 12 h before the flight for 3 days, did not prevent DVT, the low-molecular-weight heparin (LMWH), enoxaparin, at a dose of 1 mg kg^{-1}, 2–4 h prior to a long-haul flight, significantly reduced the incidence of DVT by Doppler sonography (from 4.8% to 0%) [32]. Interestingly, coagulation activation could be abrogated by injection of LMWH prior to exposure to a hypobaric chamber simulating cabin pressure [33].

In another study by the LONFLIT investigators, an oral profibrinolytic agent has proved to be useful in preventing DVT in high-risk long-haul flight passengers [34].

The Aerospace Medical Association (AsMA) has recently published guidelines for prevention of travel-related DVT [35]. For moderate risk the AsMA guidelines suggest aspirin $\pm$ graduated compression stockings. The high-risk group was defined as that having previous VTE, known thrombophilia, major surgery within 6 weeks, previous CVA, malignancy or family history of VTE. For this group, LMWH or heparin prophylaxis may be recommended by the passengers' medical practitioners [35].

As the evidence-based data are limited, consensus among experts in the field is warranted. In this issue of the *Journal of Thrombosis and Haemostasis*, Kuipers *et al.* [36] report a recent survey comparing travel-related thrombosis prophylaxis methods in attendees of three international conferences held last August in Sydney (the XXth ISTH Congress, the 15th ISDB Congress and the 13th Cochrane Colloquium). The analysis revealed that ISTH delegates used prophylactic measures more often than others and that medical doctors used LMWH prophylaxis more often than other ISTH delegates. In the survey of the medical conferences the most common risk factors were found to be estrogen use, varicose veins thrombophilia and history of VTE. Of note, anticoagulation was applied by 49% of

attendees with prior VTE and by 40% of attendees harboring thrombophilia. In contrast, only 5% of hormonal therapy users and 15% of those with varicose veins used anticoagulant prophylaxis. Moreover, only 36% of passengers with varicose veins used elastic stockings. In general, travelers with risk factors applied anticoagulation and elastic stockings significantly more often than those without risk factors (22% vs. 4% and 36% vs. 13%, respectively). In contrast, the use of aspirin was not significantly different between the groups (27% vs. 19%), suggesting either that these passengers were already on aspirin for another reason or alternatively that passengers with and without risk factors may have considered aspirin relatively harmless and potentially beneficial.

Thus, it can be concluded that the value of low-dose aspirin appears to be limited in the setting of a long-haul flight. Prospective studies with LMWH and new anti-Xa and antithrombin anticoagulants in predefined high-risk groups, such as passengers with thrombophilia or women on hormonal therapy, are highly warranted. International health organizations, aviation authorities and the airline industry should cooperate with researchers and the health industry to support these timely studies on a potentially preventable disease with a global impact.

It is of vital importance that guidelines for passengers based on risk assessment be developed and approved by expert consensus. In the meantime, passengers with risk factors should be advised on an individual basis on the potential risk of long-haul flights and available prophylactic measures.

Disclosure of Conflict of Interests

The author states that he has no conflict of interest.

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