Venous Thrombosis After Long-haul Flights

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Background: The risk for venous thromboembolism after long-haul flights represents a controversial issue. The aim of our study was to assess the incidence of venous thrombosis associated with long-haul flights in a prospective, controlled cohort study.

Methods: We included 964 passengers returning from long-haul flights (flight duration, ≥8 hours) and 1213 nontraveling control subjects. We excluded participants who were being treated with anticoagulant drugs or who used compression stockings. Main outcome measures were the incidence of ultrasonographically diagnosed thrombosis in the calf muscle and deep veins, symptomatic pulmonary embolism, and death.

Results: We diagnosed venous thrombotic events in 27 passengers (2.8%) and 12 controls (1.0%) (risk ratio [RR], 2.83; 95% confidence interval [CI], 1.46-5.49). Of these, 20 passengers (2.1%) and 10 controls (0.8%) presented with isolated calf muscle venous thrombosis (RR, 2.52; 95% CI, 1.20-5.26), whereas 7 passengers (0.7%) and 2 controls (0.2%) presented with deep venous thrombosis (RR, 4.40; 95% CI, 1.04-18.62). Symptomatic pulmonary embolism was diagnosed in 1 passenger with deep venous thrombosis (P = .44). All of these individuals had normal findings at baseline ultrasonography. Passengers with isolated calf muscle venous thrombosis or deep venous thrombosis had at least 1 risk factor for venous thrombosis (≥45 years of age or elevated body mass index in 21 of 27 passengers). The follow-up after 4 weeks revealed no further venous thromboembolic event.

Conclusions: Long-haul flights of 8 hours and longer double the risk for isolated calf muscle venous thrombosis. This translates into an increased risk for deep venous thrombosis as well. In our study, flight-associated thrombosis occurred exclusively in passengers with well-established risk factors for venous thrombosis.

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Homans12 was the first to report 2 cases of venous thrombosis after long-distance flights in 1954; in 1977 Symington and Stack3 introduced the term economy class syndrome; and in the past decade at least 200 cases of traveler’s thrombosis have been reported in the literature.7 The following pathophysiological mechanisms have been suggested: (1) cabin-related factors such as decreased air pressure and release of nitric oxide5,6; (2) dehydration as a result of the low humidity in the cabin and consumption of alcohol and caffeine during the flight7,8; and (3) venous stasis.1,8

However, the risk for venous thromboembolism after long-haul flights represents a controversial issue. Three case-control studies estimated the relative risk after long-haul flights to range from 1.0 (95% confidence interval [CI], 0.3-3.0) to 3.98 (95% CI, 1.9-8.4).9-11 The published data, drawn from case reports, retrospective analyses, or case-control studies, have been criticized because of an inadequate design or a small sample size.

A statement recently issued by the World Health Organization declared that “a link probably exists between air travel and venous thrombosis,” but “such a link is likely to be small, and mainly affects passengers with additional risk factors.”12 The authors of this statement concluded that the scientific data are presently insufficient and further studies are warranted.

See also pages 2674, 2766, and 2771

We conducted a prospective cohort study in passengers and control subjects to further elucidate the risk for thrombosis associated with long-haul flights, a study design suggested recently by McGillavry and coworkers.13 We hypothesized that isolated calf muscle venous
thrombosis (ICMVT) in the soleus and gastrocnemius calf muscles was a precursor to or the first step toward deep venous thrombosis (DVT). With ICMVT detected by means of compression ultrasonography as a surrogate marker for DVT, it should be possible to reduce the sample size for an incidence study of flight-associated thrombosis. A proof-of-concept study demonstrated the feasibility of the design and allowed sample size calculation. Venography was not performed in this study, because it is clearly not acceptable to conduct such an invasive examination in healthy, asymptomatic participants. Moreover, sufficient evidence exists that thrombi in the proximal veins and distal calf veins are readily detectable using compression ultrasonography in a vascular laboratory with well-trained investigators.

**STUDY PARTICIPANTS**

We established a cohort of flight passengers who intended to undertake a long-haul flight and a control group into the study. Recruitment of controls was stopped after the target sample size in the passenger cohort was reached. Participants were recruited by placing advertisements in travel agencies and local newspapers and via information broadcast by local television and radio networks.

**INCLUSION AND EXCLUSION CRITERIA**

Inclusion criterion in the passenger cohort was the intention to take a flight lasting 8 hours or longer without a stopover; and in the cohort of the controls, not to travel a long-distance flight 3 months after enrollment into the study. Exclusion criteria for all participants were lack of informed consent, life expectancy of less than 3 months, age younger than 18 years, use of compression stockings or elastic bandages, use of anticoagulants at therapeutic or prophylactic dosages, and thrombosis found at the baseline examination.

**EXAMINATIONS**

All examinations were performed in our vascular diagnostics unit. In the flight passenger group, the baseline examination was performed within 1 week before the outgoing flight and the second examination within 48 hours after the return flight. In the control group, the 2 examinations were performed in the same way. The duration between the visits in the control group was determined according to the results of our pilot study.

At baseline examination, the following acquired risk factors for thrombosis were assessed in all participants: age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), previous DVT, previous pulmonary embolism (PE), trauma and/or surgery 4 weeks before inclusion, active cancer, immobilization for more than 3 days in the 2 weeks before inclusion, use of oral contraceptives, hormone therapy, pregnancy, varicose veins, and family history of DVT and PE. Blood coagulation and thrombophilia screening was also performed, including levels of D dimer (elated at >0.3 μg/mL), activated protein C resistance (cutoff ratio, 2.0), factor V Leiden, G20210A prothrombin gene mutation, protein C deficiency (<70%), protein S deficiency (<70%), antithrombin III deficiency (<40%), factor VIII levels (elated at >150 IU/dL), and lupus anticoagulant levels. All flight passengers were encouraged to perform stretching exercises of the lower limbs during the flight, walk in the cabin, and drink plenty of nonalcoholic beverages.

At follow-up examination, all participants were asked about symptoms of thrombosis or PE. A questionnaire was used to obtain information not known at the baseline examination about acquired risk factors or any new medication. In addition, a second D-dimer test was performed in all participants. Finally, a 4-week follow-up was scheduled for all flight passengers and controls. All of these participants were contacted by telephone and asked about further diagnostic signs of DVT, ICMVT, PE, and death after the second examination using a questionnaire.

In both study groups, venous compression ultrasonography was performed at each presentation (HDI 5000, UM9 HDI, linear array, 4-7 MHz; ATL, Bothell, Wash; and Sonoline, linear array 7.5 MHz; Siemens, Erlangen, Germany) using a standardized examination protocol. To avoid a biased ultrasonographic assessment, ultrasonography was performed by a second physician (T.S., W.O., K.H., or J.B.), and the sonographer (T.S., W.O., K.H., or J.B.) was masked to case or control status of the participants. With the patient supine, the following venous segments were examined with B-mode compression ultrasonography: common femoral vein, proximal part of the great saphenous vein, deep femoral vein, proximal superficial femoral vein, and distal superficial femoral vein. After this, the study participant had to sit up with the legs hanging down. In this position, the following segments were examined with B-mode compression ultrasonography: popliteal vein down to the trifurcation, proximal part of the small saphenous vein, confluence segment of the posterior tibial veins and peroneal veins, proximal and distal parts of the tibial posterior and peroneal veins, lateral and medial gastrocnemius muscle veins, lateral and medial soleal sinuosids of the proximal and distal calf, and distal parts of the great and small saphenous veins. If thrombosis was clinically suspected, Doppler modalities were used for examination of the iliac veins and the inferior caval vein. The diagnostic criterion for thrombosis was the lack of compressibility of 1 or more segments of the veins of the lower extremities.

We treated DVT according to standard protocols. A 10-day course of low-molecular-weight heparin (nadroparin-calcium; 90 anti-Xa U/kg body weight twice daily) was used to treat ICMVT.

**OUTCOME MEASUREMENTS**

The primary end point of the study was the ultrasonographic diagnosis of ICMVT in the soleal and gastrocnemius muscle veins in individuals with normal findings at the baseline examination. Further end points were as follows: (1) the ultrasonographic diagnosis of DVT in individuals in whom findings had been normal at the baseline examination; (2) PE diagnosed by means of ventilation-perfusion lung scan or spiral computed tomographic scan, if clinically suspected; and (3) death, confirmed by the death certificate or necropsy.

**ETHICS**

The study protocol was approved by the institutional ethics committee of the University of Dresden Medical School, Dresden, Germany, and written informed consent was obtained from all participants.

**STATISTICAL ANALYSIS**

Sample size calculation was based on a pilot study conducted from August 1 to September 30, 2001, including 160 flight passengers and controls in which an incidence of ICMVT of 2.9% in passengers and 0.6% in controls was revealed. To detect such a difference in risks with a power of 90% underlying a significance level of 5%, 918 participants were needed in each group. A proof-of-concept study demonstrated the feasibility of the design and allowed sample size calculation. Sample size calculation was based on a pilot study conducted in 14 healthy, asymptomatic volunteers. A randomized, placebo-controlled, double-blind 4-week study was conducted in the vascular laboratory with well-trained investigators.

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Isolated Calf Muscle Venous Thrombosis

We diagnosed ICMVT in 20 (2.1%) of 964 flight passengers (13 men and 7 women) compared with 10 (0.8%) of 1213 controls (3 men and 7 women; \( P = .01 \)). An example of ICMVT in the gastrocnemius muscle vein is shown in Figure 1. In 17 of the 20 flight passengers, ICMVT was diagnosed in the soleus muscle veins; in 3, in the gastrocnemius muscle vein; and in 2, in both muscle vein groups. Nineteen flight passengers with ICMVT were asymptomatic. Mean age of all individuals with ICMVT from 8.5 to 13 hours (mean, 10 hours; SD, 2.4 hours).

In the control group, ICMVT was diagnosed in the soleus muscle veins in 8 of 10 individuals and in the gastrocnemius muscle veins in 2 of 10. All cases of ICMVT in the control group were asymptomatic. Mean age of all controls with ICMVT was 63 years (SD, 11.9 years; range, 42-82 years). The BMI was normal in 3 of the 10 controls and elevated in the other 7 (mean, 25.7; SD, 2.0; range, 23.4-29.9).
DVT and PE

We diagnosed DVT in 7 (0.7%) of 964 flight passengers (4 men and 3 women) compared with 2 (0.2%) of 1213 controls (2 men) (P = .04). In 5 of the 7 flight passengers, the thrombosis was found in the peroneal or tibial posterior veins of the calf; in 2, in the popliteal vein. In 2 passengers, symptoms of DVT were present with isolated calf pain but no differences in calf diameter. All 7 flight passengers with DVT traveled in the economy class and showed commonly known risk factors for venous thrombosis: all were of an older age, 6 (86%) showed increased BMI, 4 (57%) had elevated factor VIII levels, 2 (29%) were receiving hormone therapy, and 2 (29%) had a family history of DVT. The length of the flight in the passengers with DVT ranged from 12 to 15 hours (mean, 10.5 hours; SD, 2.17 hours).

In the control group, DVT was diagnosed in 2 individuals, including a 65-year-old man with a personal and family history of DVT who showed recurrent symptomatic, proximal DVT in the femoral superficial vein, and a 73-year-old man with an elevated BMI who showed a segmental, asymptomatic thrombus in the deep femoral vein on the upper end of a knee-bandage prescribed for gonarthrosis.

As a result, the RR for a venous thrombotic event in flight passengers was 2.83 (95% CI, 1.46-5.49); for DVT, 4.40 (95% CI, 1.04-18.62); and for ICMVT, 2.52 (95% CI, 1.20-5.26) (Figure 2). Symptomatic PE was diagnosed by means of ventilation-perfusion lung scan in a flight passenger with ultrasonographically proved thrombosis in the tibial posterior calf veins at the second examination (P = .44). In both study groups, mortality was 0%.

ALL VENOUS THROMBOTIC EVENTS

We diagnosed venous thrombotic events in 27 (2.8%) of 964 passengers and in 12 controls (1.0%) (RR, 2.83; 95% CI, 1.46-5.49). In all these individuals, findings had been normal at the baseline examination. Acquired and inherited risk factors of all participants with ICMVT and DVT in both study groups are given in Table 2.

FOLLOW-UP

The 4-week follow-up was completed in all individuals in both study groups. No further ICMVT, DVT, or PE was diagnosed within 4 weeks after the second compression ultrasonographic study. No subject died, and no major or minor bleeding occurred in participants receiving low-molecular-weight heparin or oral anticoagulants due to ICMVT, DVT, or PE.

COMMENT

The present results suggest that the incidence of ICMVT may be used as a surrogate marker of DVT associated with air travel. The natural history of ICMVT in general is not known, and the clinical significance has not been fully elucidated yet. However, ICMVT in the soleus and gastrocnemius muscle veins has been suggested as the first step toward DVT.20 The percentage of progression of muscle thrombi into the deep calf and proximal veins is also unknown. From the present data, it may be concluded that asymptomatic ICMVT in the overall population has an incidence of 1/1000 per month. This figure is obviously doubled by exposure to a pair of outgoing and return long-haul flights.
In our study, the difference in the incidence of ICMVT translates into a significant increase in risk for DVT and/or PE. However, the CI was large. A recent cohort study from our group has shown that short-term anticoagulation in ICMVT prevents thrombus progression.21 For this reason, all flight passengers with ICMVT were treated immediately after diagnosis with a 10-day course of low-molecular-weight heparin at a therapeutic dosage. Owing to this regimen, the cumulative incidence of DVT in the 4-week follow-up is likely to be underestimated. No unequivocal conclusion can be drawn regarding symptomatic episodes of venous thromboembolism.

COMPARISON WITH OTHER DATA

Previously published studies have yielded ambiguous results. Two other incidence studies have been published. Scurr and coworkers22 examined 116 passengers before the outgoing and after the return flights by means of ultrasonography and found an incidence of 10% for asymptomatic calf DVT in passengers who did not use compression stockings during the flight. However, this study was criticized because no details were provided on diagnostic criteria or thrombus localization and extension and because of a potential for bias during the ultrasonographic study.23 The first through third Long Flights Thrombosis (LONFLIT) studies showed an incidence of DVT after long-haul flights of 4% to 6%.24 In these studies, which were limited to venous ultrasonographic examination of the femoral and popliteal veins, only flight passengers were included. Again, no specifications of the ultrasonographic findings were given. Neither study allows estimation of the natural risks of air travel for the incidence of venous thrombosis, since no control group was investigated. In addition, both studies seem to overestimate the incidence of venous thrombosis in flight passengers. This is most likely due to a biased ultrasonographic examination. With a standardized examination protocol performed by masked readers, the incidence of DVT does not exceed 1%, and even for ICMVT it is lower than 3%.

A relative risk of 2 to 3 for venous thromboembolic events associated with air travel falls within the range of the figures given by 2 case-control studies for traveler’s thrombosis.10,11 However, these estimates referred to symptomatic events, whereas our RR has been found for most asymptomatic events.

LIMITATIONS

There are 3 limitations of our study that have to be considered. First, our results may not apply to the general population. Second, the baseline characteristics of passengers and controls do not match in each category. A selection bias could only have been avoided in a randomized, prospective study, but such a study design is obviously not feasible. The percentage of participants with a previous personal or family history of DVT and PE was quite high. This suggests a specific motivation to participate in our study. We therefore conclude that our study is likely to overestimate the incidence of venous thrombotic events in both groups. On the other hand, the control group consisted of significantly more individuals with personal health problems, in particular women with varicosis and venous insufficiency. Under the assumption that these conditions increase the risk for venous thromboembolic events, the relative risk for flight-associated thrombosis might be underestimated due to the increased risk for venous thromboembolism of the controls. Third, for ethical reasons, we recommended to all passengers that they consume nonalcoholic beverages and perform stretching exercises during the flight. It is conceivable that the detectable risk for thrombosis was re-

Table 2. Characteristics and Risk Factors of Flight Passengers and Control Subjects With DVT and ICMVT*

<table>
<thead>
<tr>
<th></th>
<th>Flight Passengers (n = 964)</th>
<th>Controls (n = 1213)</th>
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<tbody>
<tr>
<td></td>
<td>DVT</td>
<td>ICMVT</td>
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<tr>
<td></td>
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<tr>
<td>No. (%)</td>
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<td>20 (2.1)</td>
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<tr>
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<td>13/7</td>
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<td>66</td>
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<tr>
<td>Calf veins</td>
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<td>Proximal veins</td>
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<td>2</td>
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<tr>
<td>ICMVT</td>
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<tr>
<td>Soleus veins</td>
<td>18</td>
<td>8</td>
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<tr>
<td>Gastrocnemius veins</td>
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<td>19</td>
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<td>D-dimer result at</td>
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<td>follow-up, No. (%)</td>
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<td>Normal</td>
<td>3 (42.9)</td>
<td>13 (65.0)</td>
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<td></td>
<td>1 (50.0)</td>
<td>8 (80.0)</td>
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<td>4 (57.1)</td>
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<tr>
<td></td>
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<td>2 (20.0)</td>
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Abbreviations: APC, activated protein C; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DVT, deep venous thrombosis; ICMVT, isolated calf muscle venous thrombosis; PE, pulmonary embolism.

*Unless otherwise indicated, data are expressed as numbers of subjects.
duced in passengers who followed our recommenda-

tion. However, we could not prove how many passengers
complied with these measures. Thus, these data may also
be unreliable.

**IMPLICATIONS**

Our study strongly supports the World Health Organiza-
tion statement that there is an increased risk for ve-
nous thromboembolic events after long-haul flights, that
the relative risk is in the lower range of the established
transient risk factors, and that this applies only to indi-
viduals with preexisting permanent risk factors. Follow-
ing our data, a general prophylaxis other than stretch-
ing exercises and adequate hydration for all passengers
is clearly not mandatory. Whether passengers at risk could
potentially profit from further prophylactic measures such
as heparin therapy or compression stockings has to be
investigated in future, well-designed, randomized stud-
ies in a large study population at risk. Since the calf muscle
veins are the preferred location of the initial event of
thrombosis, ultrasonographic detection of this abnor-

mality may be used as a surrogate marker.

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