Study Supports Air Travel/VTE Link

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BOSTON — Air travel can put frequent or casual flyers at significantly increased risk for a venous thromboembolic event for up to a month after the end of a trip, British researchers reported at a meeting of the International Society on Thrombosis and Haemostasis.

Flying for more than 4 hours at a stretch—or a total flying time of more than 12 hours in the past 4 weeks—was associated with a two- to nearly threefold greater risk for venous thromboembolism (VTE), compared with nontraveling controls, reported Dr. Peter K. MacCallum of Barts and The London at the University of London.

"In this community-based case-control study, we found that air travel was a mild risk factor for venous thrombosis in the subsequent 4 weeks. The risk seen at 4 weeks was no longer apparent at the 12-week time-frame, so the dose response and the declining risk with the passage of time tend to support a causal relationship between air travel and subsequent thrombosis," Dr. MacCallum said.

The size of the air-travel effect on VTE risk was comparable to that of low-risk surgery. Other factors associated with increased VTE risk were body mass index from 25 to 30 kg/m^2, or greater than 30.

Case series linking air travel to VTE risk date to the 1950s, and by 1977 the phenomenon had been dubbed "economy class syndrome." Case-control, observational, follow-up, intervention, and laboratory studies have been conducted in the past decade, Dr. MacCallum said.

The current study findings echo those of a recent meta-analysis, which suggested that air travel was associated with about a threefold risk for VTE (Ann. Intern. Med. 2009;151:180-90).

The study showed that 'air travel was a mild risk factor for venous thrombosis in the subsequent 4 weeks,' with an effect comparable to that of low-risk surgery.

Dr. MacCallum and his colleagues studied patients in 123 general practices in the United Kingdom. They identified patients who had received a prescription for warfarin over the previous 12 months, performed a record search to identify patients with confirmed deep vein thromboembolism/pulmonary embolism (DVT/PE), and assigned six age- and sex-matched controls for each case.

The researchers contacted cases and controls by mail, and received replies from 638 cases (55%) and 3,162 controls (58%). After exclusions for various reasons, they arrived at 550 cases and 1,971 controls for the final sample (1:36 ratio).

In a univariate analysis, the only significant flight-associated risk factor for short-term VTE was total flight time longer than 12 hours (odds ratio 1.91; 95% confidence interval 1.08-3.39). In a multivariate analysis adjusted for BMI, surgery, and past history of VTE, the only significant risk factors for VTE within 4 weeks of flying were any flight leg longer than 4 hours (OR 2.20; 95% CI 1.29-3.73) and total flying time greater than 12 hours (OR 2.75; 95% CI 1.44-5.28). By week 12, neither flight leg duration nor total flight time was significantly associated with increased risk for VTE.

The authors plan to conduct additional analyses to explore the relationship between air travel and other risk factors, although they are working with fairly small samples, Dr. MacCallum acknowledged.

The funding source for the study was not disclosed. Dr. MacCallum said that he had no relevant conflict-of-interest disclosures. ■

Mutations Related to Thrombophilia Implicated as Risk Factors for VTE

BOSTON — A genomewide scan of sibling pairs from families with a genetic susceptibility to developing venous thromboembolism has identified mutations in four genes on chromosome 7 as likely genetic markers for familial thrombophilia.

Single nucleotide polymorphisms (SNPs) in the four genes were linked to familial thrombophilia syndromes. The genes, which don't overlap with genes previously linked to venous thromboembolism (VTE), may account for a large proportion of missing VTE risk factors, Dr. Marieke de Visser said at a meeting of the International Society on Thrombosis and Haemostasis.

The findings could "greatly expand our repertoire of VTE candidate genes," commented Dr. Edwin Bovill, chairman of the department of pathology and laboratory medicine at the University of Vermont in Burlington.

VTE is a multicausal disease in which both environmental and genetic factors are known to be involved, said Dr. de Visser of the department of thrombosis and hemostasis at Leiden (the Netherlands) University Medical Center.

"So-called familial thrombophilia is thought to be an oligogenetic disease in which at least two genetic risk factors are present," she said. About 30% of families with familial thrombophilia have known genetic risk factors, suggesting that a significant proportion of risk factors has yet to be identified. "The idea that genetic risk factors are missing is further supported by the observation that many hemostasis-related proteins both correlate with thrombosis risk and show high hereditability."

Investigators from the Genetics in Familial Thrombosis (GIFT) collaborative collected data on families seen at 29 Dutch anticoagulation clinics. They recruited 211 families consisting of 213 sibships, with 287 sibling pairs that included 460 siblings (87% of sibships consisted of two siblings, 19% had three siblings, and 3% had four siblings). Affected family members had confirmed VTE at or before the age of 45 years. The authors looked at data on both an index sample (two generations, 211 participants) and a nonindex sample (249 participants).

In both the index and nonindex samples, the mean age at first VTE was about 33.5 years, and 46% had more than one event. In about two-thirds of each group, the first VTE was a deep vein thromboembolism (DVT) in the leg or arm. Pulmonary embolism (PE) was the first presentation in about 20% of patients, DVT and PE occurred in about 9%, and thrombophlebitis occurred in about 9%. In nearly half of the families, at least one parent also had a VTE.

The index group had a high prevalence of genetic risk factors, including factor V Leiden in 36.5%, ABO blood group non-O (82.9%), protein S deficiency type III (10.5%), and protein S deficiency type I (7.6%).

The researchers narrowed their search down to SNPs in four candidate genes on chromosome 7: RAC1, COL28A1, NXPH1, and, most robustly, THSD7A. These candidate genes may account for many of the missing genetic factors associated with VTE risk, Dr. de Visser said.

The study was supported by grants from the Netherlands Heart Foundation and the Netherlands Organization for Scientific Research. Dr. de Visser said that neither she nor her coauthors had relevant conflicts of interest. ■

VTE Risk Rises in Tall Men, but Not In Tall Women

BOSTON — Taller men appear to have a twofold greater risk for venous thromboembolic events than do men of more modest height, Norwegian investigators reported.

Men taller than 181 cm (about 5 feet 11 inches) had double the risk of either provoked or unprovoked venous thromboembolic events (VTEs), compared with men 173 cm (about 5 feet 8 inches) or shorter, reported Dr. Knut H. Borch of the Center for Atherothrombotic Research in Tromsø, Norway, and his colleagues.

In men, each 10-cm increase in height was associated with a significant hazard ratio of 1.34. In women, height was not a significant risk factor for VTE (HR 1.13), he said at a meeting of the International Society on Thrombosis and Haemostasis.

"We suggest that body height should be considered in risk stratification of VTE," Dr. Borch said. More research is needed to determine how height interacts with other risk factors for VTE.

A 2005 analysis of data from the Physicians' Health Study (Am. J. Epidemiol. 2005;162:975-82) found that every 10 cm of height was associated with about a 36% increase in risk in men. In a separate study, Swedish researchers also found a positive association between body height and VTE risk in men (J. Thromb. Haemost. 2008;6:558-64).

Compared with men in the lowest height quartile, the hazard ratio for VTE among the tallest men was 1.99. The hazard ratio for each 10 cm of height was 1.34.

Dr. Borch and his colleagues drew data from the Tromsø Study, a prospective population-based study of men and women aged 25 years and older in the town of Tromsø, in northern Norway. The study included 26,727 residents. The researchers recorded all first lifetime VTEs from the date of study enrollment (1994-1995) through Sept. 1, 2007. Cases were identified by discharge diagnosis, autopsy registry, and radiology procedure registry. VTE was confirmed by diagnostic procedure or autopsy, and the data collected included diagnosis of deep vein thromboembolism (DVT) or pulmonary embolism, signs and symptoms consistent with VTE, and VTE treatment.

During the median follow-up of 12.5 years, there were 462 VTEs, 193 (41.8%) of which were classified as provoked (associated with major surgery or an acute medical condition within 8 weeks of the event, cancer at the time of the event, prolonged immobilization, or other known risk factors). Of the provoked VTEs, 64.3% were DVTs. Overall, the incidence of VTE was 1.6 per 1,000 person-years.

Among men, there were 219 VTEs. Men in the tallest quartile (181 cm and taller) had a significantly increased risk for VTE, vs. men in the lowest height quartile (less than 173 cm). In a multivariate analysis that adjusted for other risk factors, the hazard ratio for the tallest men was 1.99. The hazard ratio for each 10 cm of height was 1.34. Height had no effect on total VTE risk among women. In both men and women, the risks for provoked vs. unprovoked VTE were similar.

Possible explanations for the sex difference in the VTE-height relationship include unidentified sex-specific differences in venous architecture, or differences in pressure dynamics or stasis, Dr. Borch said.

The funding source for the study was not disclosed. Dr. Borch declared that neither he nor his coauthors had relevant financial disclosures. ■