Travel as a Risk Factor for Venous Thromboembolic Disease*

A Case-Control Study

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Background: **The link between travel and the risk of venous thromboembolic disease (VTED) has been widely suspected. However, only cases or series of cases have been reported in the literature.**
Study objectives: **By means of a case-control study, we sought to confirm this relationship and to determine the main features, if any, of these posttravel VTEDs.**
Design: **The history, in particular the history of recent travel, of 160 patients presenting in our department with VTED was scrupulously investigated. All journeys undertaken during the preceding 4 weeks and lasting > 4 h by whatever means of transport were considered. The same questionnaire was submitted to a control group.**
Results: **When the two groups of patients are compared, a history of recent travel is found almost four times more frequently in the VTED group ($p < 0.0001$). The odds ratio for having a VTED in patients who traveled was 3.98 (95% confidence interval, 1.9 to 8.4). Means of travel used included the train in 2 cases, airplane in 9, and car in 28. Mean duration of travel was 5.4 ± 2.1 h. These posttravel VTEDs are not confined to a specific location, seem to involve no particular predisposition, and are more often "idiopathic." This fact supports the hypothesis that travel alone can produce vein clot formation.**
Conclusions: **A history of recent travel is a risk factor for VTED. Posttravel venous thrombotic events can occur after short journeys in patients with no other risk factors or concomitant disease**
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Key words: deep venous thrombosis; pulmonary embolism; risk factors; thromboembolism

Abbreviations: CI = confidence interval; DVT = deep venous thrombosis; OR = odds ratio; PE = pulmonary embolism; VTED = venous thromboembolic disease

Although Dr. Virchow[1] described venous stasis as a major factor in venous clot formation as early as 1856, a link between the sitting position and the risk of deep venous thrombosis (DVT) was probably described for the first time by Simpson[2] in 1940. This British surgeon noticed a considerable increase in fatal pulmonary embolism (PE) in Britons forced to remain in a sitting position in cramped conditions for hours on end during the London Blitz.

Since then, many case reports dealing with the occurrence of DVT or PE after prolonged travel have been published.[3–7]

This possible connection achieved notoriety in 1988 when Cruickshank et al[8] dubbed it the "economy class syndrome," a term already used by others for a wider range of events occurring during travel in cramped circumstances.[9]

However, only case reports and retrospective series have been published so far with all the limitations inherent in this kind of data. In particular, it is still uncertain whether travel represents a risk factor for the occurrence of DVT or PE in a broad population. Also, we do not know which modes of travel might be incriminated. Similarly, we are still unaware whether venous clot formation after travel possesses particular characteristics and occurs in special circumstances.

We performed a case-control study to determine whether travel represents a risk factor for venous thromboembolic disease (VTED). In addition, we tried to determine the principal characteristics, when there were any.

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Materials and Methods

All patients hospitalized for VTED in our cardiology department were required to answer a questionnaire. The main results of this survey were published several months ago.[10] As our study took the form of an epidemiologic survey, special attention was paid to all known risks or suspected risk factors, in particular recent travel. All journeys made during the preceding 4 weeks and lasting >4 h were considered, whatever the means of transport. The questionnaire comprised >300 questions of which 12 dealt with previous history of travel (reason for travel, means of transport, distance, duration). These questions were asked at patient's bedside. Answers were entered in a database (FileMaker Pro; FileMaker, Inc.; Santa Clara, CA) for processing.

To avoid "memory bias," *ie,* distortions due to faulty recollection, questions were asked during the first few days after hospitalization then again before hospital discharge, often with the assistance of the patients' families. The same questions were put to an age-matched control group. This control group was made up of consecutive patients admitted to our cardiology department, during the same period, for the first time and for a first event. Selection bias was averted in this group by excluding patients with severe diseases that might have limited their mobility as well as those receiving anticoagulant or antiplatelet therapies.

In all patients, presenting with DVT or PE, the proximal top of the venous clot in the lower limbs was located by ultrasound-echo-Doppler examination. Furthermore, questions were asked regarding the circumstances or the causes that might have favored or induced the DVT, *eg,* postsurgery, bed rest, pregnancy, venous trauma, contraceptive pill or steroid treatment, known cancer, systemic disease, known coagulation abnormality. In addition, a coagulation search for protein C, S, or antithrombin III deficiency was made (at the time of the study, activated protein C resistance was unknown). Occult cancer was also systematically sought by means of "blood cell count," chest radiograph, abdominal examination, and pelvis ultrasound examination. Other investigations were done as required, or if one of the above suggested a possible anomaly.

From July 1992 to August 1995, 168 consecutive patients were hospitalized in our cardiology department for DVT or PE. In all cases, the final diagnosis was documented.

Eight patients died in hospital. The cause of death was the VTED for which they were hospitalized or an underlying disease. As these patients could not be questioned at hospital discharge and in order to avoid any possible memory bias, they were not included. Consequently, 160 patients who could be questioned suitably entered the study group.

The control group comprised 160 patients hospitalized for a first event other than VTED: 106 were men and 54 were women. The reasons for the hospitalization of these patients were chest pain in 121 cases, arterial hypertension in 21, and syncope in 18. None of them were treated with anticoagulants or antiplatelet agents.

Statistics

Comparisons of age were made by a Student test. Comparisons of proportions were made by χ^2 test or Fisher's Exact Test; $p < 0.05$ was considered significant. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to describe the connection between VTED and travel. OR was considered to be statistically significant when the lower limit of the 95% CI was > 1.0.

Results

The main characteristics of the two patient groups are compared in Table 1. Age and history of hypertension were similar in both groups. The study group differs from the control in that it contains fewer men, has more histories of DVT, and has a greater proportion of obese patients. The difference in gender can be attributed to the method used to enroll the control group, since the latter was recruited from a cardiology department where there is a predominance of men. The differences in DVT history and obesity are classic in patients with venous thrombosis events.

Among the study group patients, 79 experienced their VTED in well-defined circumstances (postsurgery, bed rest, known cancer), while for 81 patients, no favorable circumstance was uncovered.

Among the 160 patients with VTED, a recent journey, as defined above, was found in 39 cases (24.5%). In the control group, the "incidence" of a recently completed journey was found in 12 cases (7.5%) ($p < 0.0001$). As a result, the OR for DVT or a PE in patients with a history of recent travel was 3.98 (95% CI, 1.9 to 8.4) ($p < 0.0001$).

The time between the journey and the occurrence of first symptoms of VTED was 12.6 ± 8.9 days in the VTED group and 13.2 ± 9.6 days in the control group.

Among the 39 patients who had recently completed a journey, 9 traveled by plane for a mean duration of 5 ± 0.7 h, 28 traveled by car with a mean duration of 6 ± 2.4 h, and 2 traveled by train with a mean duration of 6 ± 0.8 h. Consequently, the total mean time of travel was 5.7 ± 2.1 h.

Comparing patients with posttravel DVT vs patients with DVT with no history of recent travel, we tried to determine whether these posttravel DVTs present any specific characteristics.

Among the 39 patients hospitalized for VTED who had recently traveled, no other etiologic circumstance or concomitant disease, as defined above, was

Table 1—*Comparisons of Main Patient Characteristics in the DVT Group and the Control Group*

	VTED Group (n = 160)	Control Group (n = 160)	p Value*
Age, yr	65.3 ± 17.0	66.0 ± 15.0	NS
Hypertension, No. (%)	19 (11.8)	29 (18.1)	NS
Sex (male), No. (%)	83 (51.8)	106 (66.2)	0.04
History of VTED, No. (%)	19 (11.8)	7 (4.4)	0.02
Obesity, No. (%)	54 (33.7)	32 (20.0)	0.01
Recent travel, No. (%)	39 (24.4)	12 (7.5)	< 0.0001

*NS = not significant.

found in 29 of 39 cases (75%), while in the remaining cases of VTED, no secondary etiology was found in 46 of 121 cases (38%) (p = 0.0001) (Table 2). Furthermore, the main characteristics in these travel and nontravel groups were similar (results not shown).

The proximal top of the venous clot in the lower limbs was situated in the calf in 9 cases, in the popliteal vein in 8, the femoral in 19, and the iliac in 2 (1 patient had a bilateral calf thrombosis, 1 had documented PE with no documented DVT). There was no difference in venous clot site between the right and left sides. Similarly, there was no difference in site between the two groups of patients with DVT (Table 3).

Discussion

A link between long journeys and occurrence of DVT or PE has been suspected for some time. Many of us can remember at least one case of severe PE occurring after travel in healthy people.[11] Several reported cases have emphasized the risk of clot formation following travel, especially air travel (probably because of the greater media interest). However, the connection has not been demonstrated conclusively by means of a well-conducted study.

In this case-control study, we confirm that travel, at least journeys lasting > 4 hours, represents a risk factor for the occurrence of VTED. In our study, the incidence of posttravel DVTs is relatively high as compared with previous reports in the literature. However, our hospital is situated close to the second busiest airport in France in an area very popular with tourists. This may explain the high incidence found. Furthermore, the previous 3 to 17% incidences of posttravel DVTs described were the result of retrospective studies in which the history of recent travel could not be investigated in sufficient detail.

Table 2—*Comparison of Results of Etiologic Search in Both Groups of DVT*

	Posttravel DVT Group (n = 39)	No Travel History DVT Group (n = 121)	p Value (χ^2 Test)
Known circumstance,* No.	9	70	NS§
Positive etiologic search, No.	1†	5‡	NS§
Idiopathic VTED, No. (%)	29/39 (75)	46/121 (38)	0.0001

*Other than recent travel.
†Protein S deficiency.
‡Protein C deficiency, n = 2; Protein S deficiency, n = 2; cancer n = 1.
§NS = not significant.

More than a century ago, Virchow[1] observed that venous stasis predisposes to intravascular deep thrombosis. In the early 1950s, Wright and Osborn,[12] using a radioactive NaCL injection in the foot veins, showed that the velocity of venous blood flow in the lower limbs is reduced by half in the standing position and by ⅔ in the sitting position. It is to be expected, therefore, that travelers who sit for long periods will be prone to DVTs. In 1954, Homans,[5] dealing with four case reports, described thrombosis of the deep leg veins due to prolonged sitting. He suggested that "prolonged dependency stasis, a state imposed by airplane flights, automobile trips and even attendance at the theater is able, unpredictably, to bring on thrombosis in the deep veins of the legs."

Stasis is increased further by pressure of the edge of a seat on the back of the calves or by sitting for long periods with legs crossed. After 1 h of quiet sitting, both a decrease in venous blood flow and a gradual rise in hematocrit with a concomitant increase in plasma protein concentration of > 25% have been described.[13] Profound inertia and passenger apathy, which reduce muscle activity and consequently venous blood flow, are undoubtedly among the causes of increased venous stasis. The problem of venous clot formation risk during air travel has been discussed extensively. It is likely that several factors contribute to this risk.

Carruthers et al[14] in 1976 demonstrated a reduction in urine output during air travel with an increase in urine osmolarity. The resulting hemoconcentration may be a significant factor in clot formation.

Simons and Krol[15] showed that healthy people exposed for 8 h to a simulated flight at an altitude of 8,000 feet and 8 to 10% humidity increased their mean plasma and mean urine osmolarity, thus indicating dehydration. This occurred despite an unusually high liquid intake (2 L).

Another factor that may contribute to venous clot formation during air travel is the decrease in endothelial spontaneous fibrinolysis when ambient O_2 decreases.[16] This phenomenon, which has been described in saphenous veins in the context of vein grafts, could also be a significant contributing factor for the occurrence of vein clot formation during air travel. In effect, a cabin altitude of 8,000 feet (2,400 m) is equivalent to cabin ambient pressure of 75 kPa. Oxygen saturation of hemoglobin in healthy people at this pressure is reported to be 90% after 30 min, with considerable interindividual variation in the response to lowered partial O_2 pressure. In particular, an 80% arterial oxygen saturation level seems usual when people are dozing off.[15]

Finally, the occurrence of DVT and PE probably constitutes one of the main medical repercussions of

Table 3—*Venous Thrombosis Site in Both Groups

	Travel (n = 39)		No Travel (n = 121)		
	Right	Left	Right	Left	p Value†
Calf, No. (%)	4 (10.2)	5 (12.8)	14 (11.5)	17 (14.0)	NS
Popliteal, No. (%)	3 (7.6)	5 (12.8)	12 (9.9)	16 (13.2)	NS
Femoral, No. (%)	9 (23.1)	10 (25.6)	20 (16.5)	28 (23.1)	NS
Iliac, No. (%)	0 (0.0)	2 (5.1)	5 (4.1)	8 (6.6)	NS
Total, No. (%)	16 (41.0)	22 (56.4)	51 (42.1)	69 (57.0)	NS

*The top of the venous clot is considered. Right + left is not equal to total number because of unreported vena cava thromboses.
†NS = not significant.

air travel. Sarvesvaran,[17] dealing with 61 deaths during air travel over a period of 3 years, reported that PE was the recognized cause of death in almost 20% of these cases, most of the fatal PE occurring in people with no medical history. However, although the literature emphasizes the risk of vein clot formation during air travel, we demonstrate, as suggested by others,[3] that this risk is not restricted to air transport alone. We show that all means of transport can be "incriminated." Furthermore, the minimal duration of travel considered in our study (4 h) is short as compared with previously reported cases in which the journey responsible for DVT often exceeded 10 h.

It would be useful to discover the occurrence of venous thrombosis proportional to different means of transport. However, this would require a prospective study comparing incidences of posttravel DVTs for each mode of travel.

Another point of interest is that many recent studies dealing with the epidemiology of venous thrombotic disease[10,18] have reported an increased proportion of unexplained DVT or PE, indicating that these venous thrombotic events occurred outside the usual acknowledged circumstances. It is possible that the increase in travel in modern society is responsible, at least in part, for these "idiopathic" venous thrombotic events.

Contrary to our expectations, we found that venous thromboembolic events occurring after travel are not confined to a specific venous site (the sitting position might have been expected to favor a calf thrombosis, in particular in the left leg, on account of the Cockett syndrome, *ie*, compression of the left iliac vein by the right iliac artery). Furthermore, these DVTs seem to involve no particular predisposition. In effect, we found no more risk factors in this group as compared with patients who experienced venous thrombosis without a history of travel.

Recently, the occurrence of DVT after travel was reported in carriers of factor V Leiden mutation.[19] After a 3-week strike among French public transport workers during the winter of 1995, two carriers of this abnormality, who had to spend several hours a day traveling in a sitting position, had DVTs as compared with five who walked. Unfortunately, not all our patients were investigated for this common predisposing factor.[20] As a result, we were unable to determine whether activated protein C resistance constituted a risk factor for posttravel DVT.

Given the low incidence of clinical signs of DVT, we can hypothesize that these diagnosed DVTs represent only the tip of the iceberg of all cases occurring after travel. It is possible, in fact, that the great majority of posttravel DVTs do not give rise to clinical symptoms (or produce a few symptoms that evolve favorably). As a result, we can assume that the bulk of DVTs remain undiagnosed.

Finally, it would be of interest to assess and compare the efficacy of suggested recommendations aimed at avoiding DVTs in passengers undertaking lengthy air or road journeys.

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