Traveling As a Risk Factor for Venous Thromboembolic Disease

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Introduction

We discuss a case of pulmonary embolism and deep venous thrombosis that illustrates risk factors for venous thromboembolic disease. The literature is rich in descriptions of such risk factors as surgical procedures, immobilization, and cancer in developing this condition. However, the association between long-distance flight and venous thromboembolism remains controversial. This case is instructive because it describes a temporal association between air travel and the onset of deep venous thrombosis in a young, otherwise healthy person, and highlights the potential importance of multiple interacting risk factors.

Case Report

A previously healthy 31-year-old woman presented to the emergency department with complaints of left calf pain and dyspnea. Two days earlier she had flown from Florida to Seattle, Washington, with a 2-hour stopover in Atlanta, Georgia. Her flight from Atlanta to Seattle lasted 5.5 hours and covered 2,700 miles (4,500 km). During the flight she noted vague bilateral calf tenderness that she attributed to cramped seating. Over the next 24 hours she experienced unusual shortness of breath, mild lightheadedness, and persistent calf tightness and cramping, worse on the left side, which were unrelieved by application of a topical analgesic. On the second morning after her arrival in Seattle, the patient walked uphill a short distance and experienced a profound exacerbation of her symptoms, falling to the ground, without losing consciousness. When paramedics arrived, she declined further evaluation. Later the same day, however, after speaking to a friend who had suffered from thromboembolic disease, she decided to seek medical evaluation in the emergency department.

The patient had no prior medical problems, no miscarriages, and no surgeries except for one elective abortion at age 17. Her medications included the oral contraceptive ortho-tricyclen-lo, which she had taken regularly since age 17. She denied tobacco or alcohol use, and had no personal or family history of blood dyscrasias, deep venous thrombosis, or pulmonary embolism. She frequently traveled long distances by car or plane for work, and she recalled calf tenderness several times in the past, most recently a few months before the current incident. In the past she attributed the calf tenderness to muscle soreness associated with wearing high-heeled shoes while traveling.

On presentation the patient was dyspneic, but not in any acute distress. Her vital signs were notable for oxygen saturation 93% on room air, heart rate 130 beats/min, blood pressure 125/91 mm Hg, and respiratory rate 22 breaths/min. Physical examination was notable for a I/VI holosystolic murmur at the left lower sternal border, lungs clear to auscultation, and diameter of the left calf greater than the right calf by 2 cm, measured 10 cm below the tibial tuberosity. Moderate tenderness was present with palpation of the left calf and upon dorsiflexion of the left foot.

Laboratory values on admission, including chemistries, hemogram, coagulation profile, and cardiac enzymes, were normal, except for a D-dimer level of 22.87 ug/mL (reference range 0–0.59 ug/mL). Electrocardiogram showed sinus tachycardia but no other abnormalities. Lower-extremity duplex revealed an occlusive thrombus in the left popliteal vein, and a computed tomography angiogram of the chest showed extensive bilateral pulmonary emboli, with near-occlusion of the right main pulmonary artery, as well as multiple satellite emboli (Fig. 1).

The patient was admitted to the medicine service for anticoagulation therapy. She was treated with intravenous heparin and transitioned to oral warfarin. An evaluation of possible inherited or acquired hypercoagulable states (including protein C, protein S, and antithrombin III deficiencies; antiphospholipid antibody syndrome; hyperhomocysteinemia; and factor V Leiden or prothrombin mutations) was negative. A transthoracic echocardiogram showed nor-
mal right and left ventricular function, uncompromised by
the substantial pulmonary artery occlusion. Prior to dis-
charge the patient had normal oxygen saturation on room
air after ambulation up 2 flights of stairs.

Discussion

The exact incidence of first-time thromboembolic dis-
ease is not known, although it is estimated at 1.92 per
1,000 persons.1 There are a number of well-established
risk factors for developing thromboembolic disease (Ta-
ble 1). Less well-established risk factors include obesity,
tobacco use, and long-distance flights. This discussion fo-
cuses on 3 risk factors: long distance air travel, oral con-
traceptives (which are particular to this case presentation),
and hypercoagulable state (which should be considered in
the differential diagnosis of any young patient who lacks
other known risk factors).

Air Travel

The patient discussed here was a healthy, active 31-
year-old woman who had few of the recognized risk fac-
tors for thromboembolic disease and who developed clas-
cic symptoms of deep venous thrombosis and pulmonary
embolism immediately after air travel that lasted more
than 5.5 hours. Long-distance flight as a cause of venous
thromboembolic disease has received substantial press cov-

ers,6 although the clinical importance of this finding is
unclear. Estimates of thromboembolic disease have ranged
widely, from fewer than 1 to over 10,000 cases per million
passengers.7 This variation is probably due to the duration
of travel, which differed from study to study, with higher
incidence reported in studies of passengers who traveled
extremely long distances, and there were no cases reported
in passengers who traveled less than 2,500 km. Lapostolle
et al have elegantly demonstrated a “dose-response rela-
tionship,” meaning that incidence of thromboembolic dis-

ers.

Table 1. Risk Factors for Venous Thrombosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tr>
<td>Advanced age</td>
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<td>Previous thrombosis</td>
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<td>Presence of a central venous catheter</td>
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<td>Immobilization</td>
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<td>Major surgery or orthopedic surgery</td>
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<td>Trauma</td>
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<td>Malignancy</td>
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<td>Oral contraceptive pills</td>
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<td>Hormone replacement therapy</td>
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<td>Pregnancy or recent delivery</td>
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<td>Genetic or acquired thrombophilia:</td>
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<tr>
<td>Factor V Leiden</td>
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<tr>
<td>Prothrombin G20210A mutation</td>
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<tr>
<td>Antithrombin III deficiency</td>
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<td>Protein C deficiency</td>
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<td>Protein S deficiency</td>
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<tr>
<td>Hyperhomocysteinemia</td>
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<td>Anticardiolipin antibody syndrome</td>
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<td>Lupus anticoagulant</td>
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<tr>
<td>Myeloproliferative disorders</td>
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<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
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<td>Inflammatory bowel disease</td>
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<td>Nephrotic syndrome</td>
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(Adapted from References 2 and 3.)
ease dramatically increases with duration of travel. It has also been suggested that modes of travel other than flight increase the risk of deep venous thrombosis and pulmonary embolism, and that travel of any type, including car and train, results in a 2–4-fold increase in risk. The magnitude of this increase is similar to that of a number of other prothrombotic risk factors, such as oral contraceptive use (4-fold risk increase) or prothrombin mutation (2.8-fold increase).9

The reasons why air travel increases risk are unclear, but possible explanations include stasis impeding venous return (perhaps exacerbated by the seat-edge), hemoconcentration mediated by dehydration in the low-humidity cabin, and low PaO	extsubscript{2} impeding antithrombotic mechanisms.10 Several small trials have found that compression stockings and low-molecular-weight heparin, but not aspirin, are effective in preventing asymptomatic deep venous thrombosis, as diagnosed via ultrasound upon disembarking. However, the efficacy and cost-effectiveness of these strategies for preventing clinical disease have yet to be determined.11,12

**Oral Contraceptives**

In the patient discussed here, the only thromboembolic risk factor other than air travel was the use of oral contraceptives since age 17. The association between oral contraceptives and deep venous thrombosis has been recognized since the 1960s, with oral contraceptives linked to a 4-fold higher risk of venous thromboembolism. The risk of deep venous thrombosis, for example, is 30–40 per 100,000 women-years in oral contraceptive users, versus 5–11 per 100,000 women-years in nonusers. This increased risk is evident by the fourth month of use, does not increase with duration of use, and disappears 3 months after use is stopped.13

Not all oral contraceptives confer the same degree of risk. Formulations with higher estrogen doses are associated with a 2-fold higher risk of venous thromboembolism, compared to those with lower estrogen doses. In addition, the type of progestin used in the formulation is important. Formulations made with third-generation progestins, such as desogestrel or gestodene, are associated with a higher risk than those made with second-generation progestins, such as levonorgestrel.13

Importantly, when risk factors are combined, overall risk increases synergistically. When air travel (2–4-fold increased risk) and oral contraceptive use (4-fold increased risk) are combined, overall risk increases 16-fold.8 Our patient had been using ortho tri-cyclen lo (25 μg ethinyl estradiol and 0.18 mg norgestimate). Based on the dosage and type of estrogen and progestin, this formulation confers a lower risk-increase than do other formulations. However, in combination with air travel it is still likely to increase the risk. Thus, the etiology of our patient’s thromboembolic event may have involved both of these interacting factors.

**Hypercoagulable State**

Given her age and the absence of other risk factors, the patient discussed here was evaluated for inherited and acquired thrombophilias. Genetic abnormalities leading to increased risk of venous thromboembolism can now be identified in 50% of patients with deep venous thrombosis.14 The most common genetic abnormality is the factor V Leiden mutation, which renders factor V resistant to inactivation by activated protein C, an endogenous regulatory factor that inhibits coagulation. This mutation is found in 3–5% of asymptomatic white patients and 12–20% of unselected patients with deep venous thrombosis.15 The next most common genetic abnormality leading to thrombophilia is the prothrombin 20210A gene mutation, which is present in 4% of unselected patients with deep venous thrombosis and 2.4% of control subjects.16 Less common thrombophilias that can readily be identified include hyperhomocysteinemia and reduced levels of protein S, protein C, and antithrombin III.2

In addition to genetic causes, an acquired autoimmune thrombophilia known as antiphospholipid antibody syndrome can also increase the risk of thrombosis.2 Antiphospholipid antibody syndrome may be suggested by an elevated activated partial thromboplastin time, and can be detected by testing for lupus anticoagulant and antibodies to anticardiolipin.

As with air travel and oral contraceptive use, overall risk of venous thromboembolism seems to increase synergistically when inherited or acquired thrombophilias co-occur with other risk factors. Among oral-contraceptive users, the risk of a thromboembolic event increases 35–99-fold in carriers of factor V Leiden mutation, 16-fold in carriers of the prothrombin G20210A mutation, 9-fold in carriers of antithrombin deficiency, and 2-fold in carriers of protein C deficiency, as compared with women who do not use oral contraceptives.13,17 Identification of these conditions by appropriate laboratory testing will facilitate targeted primary prevention efforts.

Evaluation for inherited and acquired thrombophilias by appropriate laboratory testing is warranted for the following symptomatic individuals: those without strongly predisposing medical conditions such as cancer or major trauma who experience a venous thromboembolic event before age 50; those with recurrent deep venous thrombosis or pulmonary embolism; and those with a first-degree relative who had a documented venous thromboembolism before age 50. The patient discussed was under 50, otherwise healthy, had no family history of deep venous thrombosis or pulmonary embolism, and had no risk fac-
tors other than recent air travel and oral contraceptive use. Her evaluation for thrombophilias was negative, suggesting that her thromboembolic event might have been a consequence of air travel and contraceptive use, or was simply idiopathic.

This case illustrates various risk factors for the development of thromboembolic disease, including long-distance air travel. It is important to be aware of all risk factors for this disease, especially when they occur in combination. Travelers on long-distance flights can take various measures to reduce their risk: ensure adequate fluid intake, minimize consumption of alcohol and caffeine (to avoid the diuretic effect of these substances), ambulate in the aisle of the aircraft, perform stretching exercises every 2–3 h, wear compression stockings (knee-high, 30–40 mm Hg), or take low-molecular-weight heparin. The relative efficacy of these measures awaits formal evaluation.

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REFERENCES


