Air travel is associated with a risk of deep vein thrombosis and pulmonary embolism, which may be fatal. The exact incidence of thromboembolism in relation to air travel is uncertain, though it has been estimated that at least 5% of all cases of deep venous thrombosis may be linked to air travel. The term “economy class syndrome” has been coined to describe the phenomenon, and this also emphasizes the role of impairment of venous circulation due to prolonged immobility in a cramped position, in the pathogenesis of the thrombosis. A number of risk factors specific to air travel are recognized, including immobility (leading to stasis in the lower limbs and hemoconcentration), compression of the popliteal vein by the edge of the seat, and dehydration. However, inherited hematological abnormalities may also predispose to thrombosis. This article reviews the pathophysiology of venous thrombosis, and gives advice on prevention as well as guidelines on the management of established thromboembolism.

Air Travel and Thrombosis

There are many published reports which link venous thromboembolism with air travel.1–4 The first report concerned that of a physician who traveled from Boston to Venezuela in 1946 on a nonstop flight lasting 14 hours.5 The development of thrombosis in the setting of flight has been euphemistically termed the “economy class syndrome,” reflecting the importance of sitting for long periods in cramped conditions in the pathogenesis.6,7 However, venous thrombosis is not exclusively associated with air travel; it has also been documented following long car, bus or even train journeys.5,8,9 A case-controlled study from France reported a history of recent travel (with a journey exceeding 4 hours) in 39 of 160 patients with thromboembolism, of whom 9 had flown, 2 had traveled by train and 28 by car. Furthermore, thrombosis is by no means restricted to those in the relatively confined conditions of economy class, and thus the alternative term of “travelers’ thrombosis” has been suggested.10 The risk of thromboembolism associated with confinement in cramped conditions has been recognized for some years. Simpson, the distinguished forensic pathologist, noted a rise in the incidence of sudden death from pulmonary embolism associated with the onset of the night bombing raids on London at the beginning of the Second World War.11 These deaths usually occurred in elderly people who had spent a night sleeping uncomfortably in deck chairs, in an air raid shelter. Simpson recognized that the primary cause was mechanical impairment of venous circulation due to squatting for a prolonged period, and he recommended that bunks should be installed in the shelters.

The incidence of symptomatic venous thromboembolism in association with air travel is low, although no prospective studies have been conducted to quantify the risk with precision. However, even though the risk is low, the sheer numbers of passengers traveling magnifies the effect so that significant numbers of cases will be encountered in clinical practice. Two studies from Hawaii, a destination accessible only by air, with a typical journey time of over 5 hours, uncovered air travel as a risk factor in 44 of 254 (17%) patients with thromboembolism in one study,2 and in 33 of 134 (24%) in the other.3 Most reports involve venous thrombosis in the lower limbs, but there are also reports of cerebral venous thrombosis,12 and arterial thrombosis,13–15 associated with long flights. Venous thrombosis in the lower limbs can be confined to the superficial leg veins, or may extend to involve the deep veins of the calf, or the more proximal veins such as the superficial femoral, common femoral, or even the iliac veins. Thrombosis is significantly more common in the left leg, probably due to the fact that the femoral artery on that side passes anterior to the vein and may compress it. Thrombosis in the superficial veins of the legs often occurs in varicosities, but is usually self-limiting. By contrast, the risk of pulmonary embolism is much higher when proximal veins are involved. In addition to the potential for embolism, organization of the venous thrombus in the leg can ultimately cause long-term problems including chronic ulceration (post-phlebitic syndrome).

It is possible to derive some general conclusions from a survey of published cases.4 Thromboembolism is rarely observed after flights of 5 hours duration, and typically the flights are of 12 hours duration or more. The risk rises with age, and older subjects over the age of 50, are more
at risk, while those under the age of 40 years, are less vulnerable. Symptoms of thromboembolism do not usually develop during, or immediately after the flight, but more typically appear within 3 days of arrival, when the patient may present far away from the airport, and thus the causal link may not be immediately apparent. Symptoms of thrombosis or pulmonary embolism have been reported up to 2 weeks after a long flight. Pulmonary embolism may also be the first manifestation, without any symptoms in the lower limbs. In a study of 61 cases of sudden death in airline passengers on flights arriving at Heathrow airport in London between 1979 and 1982, pulmonary embolism was identified as the cause at autopsy in 11 (18%) cases. Ten cases had involved flights of longer than 12 hours duration.

Risk Factors

A number of risk factors have been recognized, primarily through clinical experience in the setting of surgery, which predispose to venous thromboembolism. These are listed in Table 1.

Smoking, contrary to popular belief, is not a risk factor for venous thromboembolism. Indeed, there is some evidence from surgical studies that it may confer a degree of protection, possibly related to a vasoconstrictive effect mediated through nicotinic receptors on the surface of smooth muscle cells. Obesity is also not a clear risk factor, although mobility will be particularly restricted in normal airline seats.

There are also risk factors specific to air travel, including relative immobility for a prolonged period in a cramped position. Both unusually tall, and short individuals, are particularly vulnerable. Most airline seats have fairly rigid metal frames designed for safety in the event of an accident, but the metal bar at the front edge may compress the popliteal vein. Dehydration is also a problem, as cabin air is derived from the cold, dry external air at high altitude, which is sucked in, and compressed by the engines, before being pumped into the cabin, after heating. Excessive consumption of alcohol will also contribute to the development of dehydration through its diuretic effect, and the sedative effect will also encourage immobility.

Thrombophilia: Inherited Predisposition to Thrombosis

An efficient system is required to stop bleeding after injury to tissues or blood vessels. The principal reaction in the clotting mechanism at the site of injury involves, the conversion of soluble fibrinogen by thrombin, to insoluble strands of fibrin, in which platelets become enmeshed. The primary physiological trigger of the coagulation cascade is the liberation of a protein, tissue factor, from injured tissues, which binds to factor VII in the circulation, leading to its activation. In turn, the tissue factor-factor VIIa complex, directly activates factor X, which forms a complex with factor V, in the presence of calcium, to convert prothrombin to thrombin. Coagulation occurs continuously at a low level throughout the vascular tree. It is, therefore, important that mechanisms exist to oppose coagulation, to damp down the coagulation cascade, and to limit both the location and extent of the clotting process to biologically appropriate sites. Natural anticoagulants in the body include both protein C and its co-factor, protein S, whose primary role is to catabolize coagulation factors V and VIII.

In some patients, a hematological abnormality may exist which predisposes to the development of thromboembolism. Such disorders include congenital, inherited deficiencies of a natural anticoagulant, such as antithrombin, protein C, or protein S. Congenital deficiencies of these three natural anticoagulants are relatively rare, each affecting perhaps 1 in 10,000 of the general population. By far the commonest genetic abnormality which predisposes to thrombosis is the factor V Leiden genotype, which is associated with resistance to activated protein C. The defect involves a single mutation in the factor V molecule (Arg 506→Gln), which renders the molecule resistant to cleavage by protein C. This mutation is encountered in approximately 4% of the white population, although it is very rare, or even absent in other racial groups. It is associated with an approximately eight-fold increased risk of venous thrombosis, but with a considerably higher risk in women taking estrogen-containing oral contraceptives. Elevation of the plasma prothrombin level, in association with a point mutation at nucleotide 20210 G→A in the prothrombin gene, is another newly identified genetic risk factor for venous thrombosis, encountered in approximately 2% of the population, and is associated with an approximately three-fold risk of thromboembolism.

**Table 1** Risk Factors

| Age: greater than 40 years (especially the elderly) |
| Previous thrombotic episode (especially pulmonary embolism) |
| Documented thrombophilic abnormality (e.g., antithrombin deficiency) |
| Other hematological disorders (polycythemia and thrombocytopenia) |
| Pregnancy and puerperium |
| Malignancy |
| Congestive heart failure or recent myocardial infarction |
| Recent surgery (especially lower limb) |
| Chronic venous insufficiency |
| Estrogen therapy (e.g., oral contraceptive pill) |
| Dehydration (diarrhea) |
In addition to these inherited defects, the development of a lupus anticoagulant is associated with an increased risk of venous thromboembolism. Although first identified in subjects with systemic lupus erythematosus, the defect occurs commonly in otherwise healthy individuals. Paradoxically, the presence of a lupus anticoagulant, which is associated with a prolonged activated partial thromboplastin time (APTT) in the laboratory, is not associated with bleeding, but with a thrombotic tendency (probably due to damage of endothelial cell surfaces). Other hematological disorders associated with an increased risk of thrombosis include the myeloproliferative syndromes, such as polycythemia and thrombocythemia.

Consideration should always be given to screening patients with venous thromboses for defects which might predispose to thrombosis. The existence of such defects may well influence the management of the patient, and identification of underlying causes such as antithrombin deficiency should be followed up by screening other family members to identify others at risk. However, deep venous thrombosis is a common problem, and it is often not feasible to screen all those who have experienced a single episode. Table 2 lists categories of patients who should be selected as a priority for investigation for possible underlying thrombotic disorders.

It is not possible to carry out testing for all thrombophilic defects while being treated with either heparin or warfarin. Both protein C and S, for example, are vitamin K dependent proteins, and plasma levels fall while on warfarin. Testing should be postponed until the patient has been off anticoagulant therapy for at least a month.

The influence of the various risk factors is demonstrated by the findings of a recent uncontrolled, retrospective study of 20 subjects who presented with deep vein thrombosis and in whom there was a history of recent air travel. Six subjects were found to have an inherited thrombophilic defect (five of whom were heterozygous for the factor V Leiden defect). Other risk factors were identified in 10 subjects, including 5 women taking an estrogen-containing contraceptive pill, 2 taking postmenopausal hormone replacement therapy, 1 woman who had traveled a few days after giving birth, 1 patient had traveled with a leg in a plaster cast, and 1 woman with malignant disease.

**Diagnosis**

It must be emphasized that one cannot not always rely on clinical examination alone to exclude the diagnosis of venous thromboembolism in the lower limbs, and there may be no obvious abnormality, even when extensive thrombosis is present. The principal tools used for objective diagnosis are contrast venography and ultrasonography. Contrast venography is regarded by many as the definitive method, and will identify thrombosis confined to veins of the calf, as well as the larger proximal vessels. However, it may be difficult to arrange this investigation at short notice. Compression ultrasonography is, therefore, increasingly preferred for initial screening, though it is of limited value in detecting thromboses confined to the calf. In this technique, the proximal veins are compressed gently using the ultrasound transducer. Inability to occlude the vein indicates the presence of a venous thrombosis. Thrombosis confined to calf veins may be missed with ultrasonography alone. Such a thrombus may extend proximally over the ensuing days, with a risk of pulmonary embolism.

More recently, measurement of the level of D-dimers in the blood has been developed as a complementary test to detect deep vein thrombosis. D-dimers are degradation fragments of fibrin, of which a thrombus is composed, and sensitive tests have been developed that may be used as an initial screening procedure for thromboembolism. The test has a high negative predictive value, and thromboembolism can be excluded with a high degree of confidence if the level of D-dimers in the blood is low. The result can be available within as little as 40 minutes after venepuncture, so it is a test of practical value. A combination of the two tests can be used to identify thrombosis in almost all cases.

**Treatment**

The conventional approach to the treatment of venous thromboembolism involves anticoagulation with heparin and, subsequently, warfarin (or other similar coumarin, such as nicoumalone). The primary purpose of anticoagulation is to prevent extension of the thrombosis due to sludging of the circulation in the area of the thrombus. Initial therapy with warfarin alone is associated with an unacceptably high rate of extension, or recurrence of thrombosis. Current accepted therapy involves the initial administration of heparin, which acts immediately as an anticoagulant. The use of standard, unfractionated heparin needs to be monitored by daily

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**Table 2. Criteria for Patient Selection for Possible Underlying Thrombotic Tendency**

<table>
<thead>
<tr>
<th>Criteria for Patient Selection for Possible Underlying Thrombotic Tendency</th>
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<tbody>
<tr>
<td>First episode of venous thromboembolism before the age of 45</td>
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<tr>
<td>Recurrent venous thrombosis</td>
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<tr>
<td>Arterial thrombosis before the age of 30</td>
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<tr>
<td>Thrombosis in an unusual site</td>
</tr>
<tr>
<td>Relatives of those with documented thrombophilic defect</td>
</tr>
<tr>
<td>Unexplained and isolated prolongation of the APTT</td>
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measurement of the activated partial thromboplastin time (APTT). This is necessary because the anticoagulant response to heparin varies considerably from individual to individual, and the anticoagulant efficacy in any individual cannot be predicted on the basis of units/kg given.

More recently, there has been a tendency to use low molecular weight heparins in preference to standard, unfractionated heparin, for initial anticoagulation. These compounds are produced by controlled chemical, or enzymatic degradation of standard unfractionated heparin. Advantages over standard heparin include the considerably greater bioavailability after subcutaneous administration, and a longer plasma half-life. The biological effect is also more predictable, so that monitoring in a hematology laboratory is not usually required after a standard dose based on body weight. A number of large clinical studies have shown that these newer, but more expensive products, are at least as safe and effective as conventional heparin, and there is also some evidence, that the incidence of heparin-induced thrombocytopenia is lower. Furthermore, they are effective when administered by single daily subcutaneous injection, and this has encouraged out-patient treatment.

Our standard approach for the treatment of established venous thromboembolism is to initiate treatment with dalteparin either as a single dose of 200 IU/kg or 100 IU/kg twice daily (with a maximum daily dose of 18,000 units). Warfarin treatment is started at the same time. Treatment with dalteparin should continue in parallel with oral anticoagulation for 5 days, or until the International Normalized Rate (INR) is more than 2.0, whichever is longer. In the case of an isolated venous thrombosis in the leg, without accompanying pulmonary embolism, warfarin treatment is continued for 3 months, aiming to keep the INR at 2.5. If there is evidence of pulmonary embolism, it is recommended that anticoagulation with warfarin continues for 6 months. Treatment with warfarin can be stopped abruptly. Tailing off of therapy was recommended, in the mistaken belief that abrupt discontinuation of treatment with warfarin was associated with a rebound hypercoagulability, but it is not necessary.

Anticoagulation is associated with a small, but definite, risk of bleeding complications such as intracranial hemorrhage. There may be cases where it would be unwise to initiate anticoagulation because of a significant risk of hemorrhage. Such situations include severe and uncontrolled hypertension, recent hemorrhagic stroke, recent surgery, peptic ulceration, esophageal varices, proliferative retinopathy, and dementia. The risk of hemorrhagic complications is greatest in patients who are excessively anticoagulated with an INR greater than 5.0, and this emphasizes the need for continued laboratory control while away from home. Anticoagulation with warfarin does not pose any particular problems for passengers, but patients should ensure that they take adequate medication with them. If traveling on a long journey, perhaps with connecting flights, the tablets should be carried in the hand luggage. If staying abroad for an extended period, arrangements should be made to have the usual periodic blood test to check the INR. Changes in diet, new medications, and an increase in alcohol consumption may affect sensitivity to warfarin, and illnesses such as diarrhea, or vomiting may impair absorption of the drug.

Anticoagulation with warfarin, or similar drugs, has implications for the flight crew. The risk of potential incapacitation due to intracerebral, or other hemorrhage, is not compatible with the granting of an unrestricted Class 1 Medical Certificate to a pilot. The identification of an underlying thrombophilic defect in a pilot who has experienced a single episode of venous thromboembolism does not ipso facto rule out certification, once a course of warfarin therapy has been completed, although long-term warfarin therapy is likely to be recommended after two thromboses.

Prevention

A number of general measures may be taken to minimize the risk of thrombosis associated with long air journeys. Adequate hydration should be ensured during the flight. It is not necessary to abstain from alcohol, but excessive consumption should be avoided, as this will both promote diuresis, and discourage mobility. Simple stretching exercises during flight, such as flexion and extension of the ankles, will help to promote circulation in the lower limbs, and occasional short walks in the cabin are recommended. Deep breaths assist the venous return, and the pulmonary circulation. Although, in recent years, the pitch of some aircraft seats has been increased, and adjustable foot rests have been installed, mobility is still restricted. An aisle seat, or one next to an exit, offers more space, although the latter are usually only allocated to able-bodied individuals in case passenger assistance is required to open doors in the event of an emergency. Hand luggage stowed under seats will also restrict movement.

In the absence of randomized controlled studies, it is not possible to give evidence-based recommendations regarding prophylactic treatment to prevent thromboembolism, but nevertheless some conclusions may be drawn from experience in other settings (Table 3). For people regarded to be at risk of thrombosis, the wearing of elasticated stockings on both legs may be helpful, and these are cheap and readily available without prescription. The stockings should extend above the knee, and care should be taken to ensure that they do not slip...
and cause constriction in the popliteal area. Quite apart from reducing the risk of thrombosis, elasticated stockings help to prevent edema in the legs and feet, which can itself cause discomfort. Since major surgery, particularly orthopedic, is a well recognized risk factor for thrombosis, it may be advisable to postpone nonessential journeys immediately after such an operation. For individuals with a definite thrombotic risk, for example a history of thrombosis and an identified thrombophilic defect such as protein C deficiency, it would be prudent to get a single injection of low molecular weight heparin by subcutaneous injection, immediately before the flight. The precise dose varies according to the particular product used, but a suitable prophylactic dose of dalteparin is 2,500 units by subcutaneous injection, 1 or 2 hours before flight. Care should be taken to avoid inadvertent intramuscular injection, as this is likely to result in the formation of a significant hematoma. Heparin should not be used when there is a pre-existing hemorrhagic condition (e.g., thrombocytopenia), or other medical condition where there is a potential for bleeding (e.g., peptic ulceration). Stockings, of course, represent a perfectly safe alternative in such cases.

The use of aspirin has been advocated for general prophylaxis by some. Aspirin is certainly a potent antiplatelet agent, and has a definite role in preventing thrombosis in the arterial tree (such as transient ischemic attacks, or myocardial infarction). However, platelets play only a minor role in the development of venous thrombosis. A meta-analysis of 55 clinical studies involving some 8,500 patients showed that aspirin is of some prophylactic value, and reduced the risk of venous thromboembolism by around 25% in a predominantly surgical setting. This degree of risk reduction is certainly significant, but is considerably less than can be achieved with heparin, or even compression stockings. A more recent, and larger prospective study, demonstrated a similar reduction in the incidence of venous thromboembolism, when aspirin was used in the setting of hip fracture during major orthopedic surgery. On balance, a single aspirin tablet taken prior to a long flight may be of some prophylactic value and is primarily suitable for individuals with no documented high-risk factors. Aspirin, in contrast to warfarin, is not contraindicated for flight crew. Aspirin is certainly not contraindicated in subjects already using low doses of heparin for thromboprophylaxis, but the combination is probably best avoided in this setting, in order to avoid the potential for hemorrhagic complications. Elasticated stockings, or low molecular weight heparin, should be considered by individuals considered to be at moderate or high risk of thromboembolism, by virtue of their medical history.

References


Table 3  Guidelines for Advice to Passengers

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prophylactic Measures to be Considered for Long Haul Flights:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complaint of leg edema without history of venous thrombosis</td>
<td>1. Exercise legs (including walking around the cabin) and deep breathing at regular intervals. 2. Keep well hydrated using clear fluids. 3. Avoid excessive alcohol. 4. Avoid sleeping in an uncomfortable position, especially with hypnotics. 5. Consider use of low compression stockings.</td>
</tr>
<tr>
<td>History of previous venous thrombosis and/or thrombophilia</td>
<td>1. Aspirin. 2. Bilateral stockings covering foot to above knee. 3. Low molecular weight heparin before flight.</td>
</tr>
<tr>
<td>Recent surgery/injury to lower limbs</td>
<td>Advise patient to avoid journey. If not, prophylaxis essential in view of high risk.</td>
</tr>
</tbody>
</table>