Current Practice

DISEASES OF THE HEART AND BLOOD-VESSELS

Venous Thrombosis

R. L. RICHARDS,* M.D., F.R.C.P.GLAS., F.R.C.P.ED.

Thrombosis may occur in any vein, but in clinical practice the problem of venous thrombosis is most often encountered in the lower limbs. In the United States, in particular, it is usual to distinguish two types of venous thrombosis, *phlebothrombosis*, in which the thrombosis is a simple non-inflammatory process, and *thrombophlebitis*, in which the thrombosis is due to or accompanied by a local inflammatory reaction in the wall of the vein. It is doubtful whether this classification is helpful either diagnostically or therapeutically. A more useful subdivision is into cases in which thrombosis is confined to superficial veins and those in which deep veins are involved.

Aetiological Factors

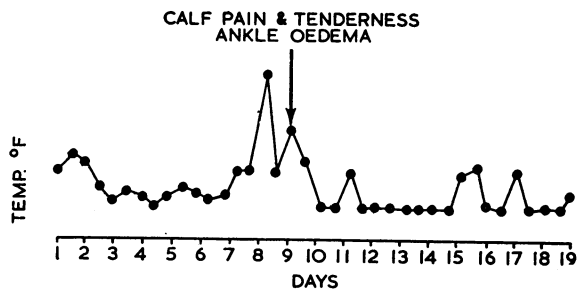
Thrombosis probably never occurs in a normal vein with normal blood-flow, though occasionally one encounters a patient with an apparently spontaneous venous thrombosis in whom no obvious aetiological factor can be found. Some of these cases occur after strenuous muscular activity, and they are particularly common in tall men.[1] Most cases of venous thrombosis occur in circumstances in which it is obvious that there is an abnormality of the vein, a slowing of the blood-flow, or some qualitative alteration of the blood, or any combination of these factors. The commonest and most obvious example of this is varicose veins, in which the vein is clearly abnormal and the blood-flow sluggish. Any external pressure upon a vein with its relatively thin wall and low intravascular pressure will impede the blood-flow and cause thrombosis distal to the obstruction ; pelvic tumours and the gravid uterus are common examples of this. The greater incidence of deep venous thrombosis in the left lower limb is thought to be due to the fact that the anatomical relations of the left common iliac vein make it more subject to compression than the right.

Bed rest is a well-known cause of venous thrombosis in the lower limbs. The loss of the normal pumping activity of the muscles of the legs, leading to slowing of the venous flow, is only one of the factors concerned. The veins in the calf muscles, particularly in soleus, are easily traumatized and form a dependent pool of stagnant blood when a patient is supine, so that thrombosis readily occurs and spreads to involve the posterior tibial and popliteal veins. The other common site for thrombosis to start in a bed-ridden patient is in the common femoral vein just distal to the inguinal ligament, as this is the lowest point in the venous system of the lower limbs in a supine or semi-recumbent patient. After surgical operations, and in cases of trauma, other factors as well as bed rest are important ; alterations in the coagulation mechanism of the blood which favour thrombosis take place,[2] and the immobility of an injured or paralysed limb may further predispose to thrombosis. Thrombosis not infrequently occurs in a vein which has been used for an intravenous infusion. Though this type of thrombosis is commonly attributed to a chemical cause, either from the infused fluid or the type of tubing used, a recent critical study suggests that a low-grade bacterial infection is often responsible.[3] In patients with cardiac failure a sluggish peripheral circulation and oedematous limbs add to the factors conducive to thrombosis ; and patients with some types of carcinoma are particularly prone to develop venous thrombosis, probably as a result of some change in the blood, though no consistent alteration in the coagulation factors has been found in such cases. Venous thrombosis in either a superficial or a deep vein is sometimes the presenting feature in polycythaemia vera. Obesity and advancing age are general factors which favour the occurrence of venous thrombosis.

Clinical Features

When thrombosis occurs in a superficial, usually varicose, vein the diagnosis is simple. The thrombosed vein can usually be seen, and if not is easily felt ; the signs of inflammation if present are clearly centred on the thrombosed vein.

The recognition of a deep-vein thrombosis is more difficult but more important, since it is this type of lesion which can lead to pulmonary embolism. It is a mistake to assume that deep venous thrombosis is a condition which occurs only in hospital, or that a patient has to be in bed for many days before venous thrombosis can occur. Pathological studies indicate that thrombi are present in the calf veins in many patients who have been in bed for only four days, and in about 75% of those who have been in bed for a week. The first clinical indication is often a rise of temperature (see Fig.).



Temperature chart showing elevation of temperature 24 hours before the presence of local signs in the leg.

This may precede the local signs by 24 hours, and it is wise to regard any otherwise unexplained pyrexia in a patient who has been in bed for more than a day or two as a possible indication of deep-vein thrombosis. Of the local signs a minimal degree of ankle oedema, confirmed by measurement of the circumference of the ankle, is the most reliable.[4]

* Consultant Physician, Western Infirmary, Glasgow.

Tenderness on deep palpation of the calf, in the popliteal space, or along the line of the femoral vein, and an increase in the skin temperature of one limb compared with the other, are other valuable signs. The popular Homans's sign (pain on forcible passive dorsiflexion of the foot) is positive in only about 10% of proved cases. By the time there is obvious swelling of the limb a well-established and extensive thrombosis is present. Unfortunately, even with the utmost vigilance it is impossible to diagnose all episodes of deep-vein thrombosis, because many incidents (according to post-mortem statistics about 66%) are "silent," and the first clinical indication of their presence may be pulmonary embolism. Additional diagnostic aids have not so far proved helpful, but a recently described technique, which uses fibrinogen labelled with iodine-125 and scintillation-counting to detect thrombi in the early stages of their formation, may prove useful.[5]

Treatment

Prophylaxis

Much has been written about the prevention of deep venous thrombosis. There is no doubt that unless there are important reasons why a patient should be confined to bed he should be encouraged to get up and to walk about. Unfortunately, both the design and the discipline of many hospital wards make this difficult. To get a patient to sit in an armchair by his bedside is probably as bad as, if not worse than, keeping him in bed. If he has to be in bed then regular exercises for the lower limbs should be instituted. It is important that the correct type of exercise should be prescribed; the usual instructions to keep moving the toes are useless; the exercises should encourage movement of the whole limb and particularly of the calf muscles. Breathing exercises are also valuable, as they encourage a better venous return to the heart. The wearing of elastic stockings by patients while they are in bed is said to be helpful; compression of the veins increases the linear velocity of blood-flow.[6]

In cases in which such simple measures are not possible but the patient will have to spend more than three or four days in bed prophylactic anticoagulant therapy should be seriously considered. Because of the difficulties and the risks inherent in the use of anticoagulants it is not possible to treat all such patients, and some degree of selection is necessary. There is good evidence from clinical trials that prophylactic anticoagulant therapy is of value in the following groups of patients:

(1) Elderly patients with fractures of the hip,[7] and probably other patients over the age of 40 with injuries who are to be in bed for more than two or three days.[8 9] Anticoagulants should not, however, be given to patients with injuries of the head, thorax, spine, or abdomen, nor to those with extensive burns.

(2) Post-operative patients over the age of 40 who have had a major gynaecological operation, and all those who have had caesarean section, an operation for malignancy of the genital tract, or a history of a previous thrombosis.[10 11]

(3) General surgical patients over the age of 40 who have had a major operation, particularly if they are obese, have pre-existing vascular disease, or have had an operation for a malignant neoplasm.[12]

(4) Patients with congestive cardiac failure. Thromboembolic episodes are frequent in such patients and often contribute to a fatal outcome.[13]

It has to be admitted, however, that in spite of the evidence in favour of giving such patients prophylactic anticoagulants I am aware of only a few centres in the United Kingdom in which this form of treatment is current practice.

If prophylactic anticoagulants are to be given in such cases they should be started immediately—that is, as soon as the injured patient's condition has been assessed—on the first post-operative day in surgical cases and as soon as possible in the patient with cardiac failure. Treatment should be continued until the patient is fully ambulant.

Superficial Venous Thrombosis

The patient who has thrombosis of a superficial vein only, without any sign of involvement of the deep veins, should not be put to bed and does not require anticoagulants. Such a patient should be provided with a firm support in the form of a crêpe bandage or elastic stocking, and should be encouraged to remain active. If there is a marked inflammatory response then a soothing local application and a short course of phenylbutazone, 200 mg. thrice daily for three days, followed by 100 mg. thrice daily for a further four days, should be prescribed. If other circumstances require that the patient should be in bed then anticoagulant therapy becomes essential, because under these conditions there is a definite risk that the condition will spread to involve the deep veins. Surgical treatment is not indicated in most cases of superficial vein thrombosis, but operation has been advocated in cases in which a thrombus in the long saphenous vein extends to within 5 to 8 cm. of the sapheno-femoral junction. The operation recommended is ligation and division of the long saphenous vein with excision or stripping of the diseased vein.[14]

Deep-vein Thrombosis

Though there are no well-controlled clinical trials of anticoagulant therapy in the treatment of established deep-vein thrombosis, it is generally accepted that the patient who has signs suggestive of such a lesion should receive this treatment unless one of the recognized contraindications is present. The results obtained by many workers indicate that efficient anticoagulant therapy reduces the risk of pulmonary embolism, and probably lessens the extent of the morbidity from the venous thrombosis itself. The patient should be put to bed, and if possible the lower end of the bed elevated so that the foot and leg are above heart level. Anticoagulants should be started immediately. Rest in bed is continued until the local signs have subsided. The patient can then be allowed up, with a firm crêpe bandage or an elastic stocking to control any local oedema. Anticoagulant therapy should be continued at least until he is fully ambulant, a period of two to three weeks in most cases.

There is suggestive evidence that, even in cases of deep-vein thrombosis where there has not been overt evidence of pulmonary embolism, repeated small pulmonary emboli may have occurred, and that such emboli may continue to arise for some considerable time after all local signs of active thrombosis in the leg have disappeared. This may lead later to the development of thrombogenic pulmonary hypertension and cardiac failure. For this reason it has been suggested that in all cases of established deep venous thrombosis anticoagulant therapy should be continued for at least six months.[15]

The use of thrombolytic agents such as streptokinase in cases of deep-vein thrombosis has given encouraging results, but the treatment is expensive and the technique of administration is complicated; this form of treatment is still in the experimental stage. Trypsin has also been used as a thrombolytic agent in these cases, but the results have not been impressive.

Surgical treatment for deep-vein thrombosis has not been widely practised in this country, but in the United States and elsewhere many believe that proximal vein ligation is a better method of preventing pulmonary embolism than anticoagulant therapy. Since it is known that, even though the signs may be unilateral, a thrombus is frequently present in both limbs, the

operation consists of either bilateral ligation of the femoral veins or ligation of the inferior vena cava.

Anticoagulant Therapy

It would be out of place in an article of this nature to discuss anticoagulant therapy in detail, but a few practical points in relation to its use in venous thrombosis can be given. For prophylactic use heparin is unnecessary: one of the oral anticoagulant drugs, preferably warfarin, should be used. An initial dose of 30 to 50 mg. of warfarin should be given whenever the decision to start treatment is made, and subsequent dosage determined by the results of whichever laboratory test is used for control. In established deep-vein thrombosis heparin should be given in an initial intravenous dose of 15,000 units, followed by 10,000 units at intervals of four to six hours. Whether to continue with heparin alone or to change to an oral anticoagulant is largely a matter of personal preference. Many surgeons believe that heparin is the better anticoagulant in these patients and continue with it for 10 to 14 days, which is often as long as is thought necessary. There is good evidence that treatment with heparin is followed by rapid improvement in the local clinical signs,[16] but the risks of bleeding with prolonged heparin treatment are undoubtedly greater than with oral anticoagulants.

If the policy is to use heparin only for its immediate effect, and to maintain therapy with an oral drug, then the loading dose of the latter should be given at the same time as the initial dose of heparin. In these circumstances heparin can be stopped when the results of laboratory tests show that the depression of the coagulation factors has reached the so-called " therapeutic level." As far as laboratory tests are concerned there is little to choose between them, and the decision whether to use the " Thrombotest " or Quick's one-stage " prothrombin time " is a matter of personal preference. If the former is used the therapeutic level to be aimed at is 5 to 10% ; if the latter, two to three times the normal.[17]

Special Types of Venous Thrombosis

Thrombophlebitis Migrans

In this condition there are recurrent episodes of thrombosis affecting short lengths of superficial veins, usually in the extremities, but also sometimes on the trunk. Deep-vein thrombosis is uncommon and pulmonary embolism is rare. In some of these cases arterial lesions are also present, and then the diagnosis is thromboangiitis obliterans ; others are associated with carcinoma, but many of the patients continue to have intermittent attacks of superficial thrombophlebitis for years without other manifestations. There is no good evidence that anticoagulants modify the course of this condition, and apart from the use of phenylbutazone as an anti-inflammatory agent in severe attacks no special treatment is necessary in most cases.

Axillary Vein Thrombosis

Spontaneous thrombosis of the axillary or subclavian vein, often associated with effort (Paget-Schroetter Syndrome), occasionally occurs in fit young persons. The symptoms are swelling and a feeling of tightness in the arm with cyanosis of the hand. Early treatment with elevation of the limb and anticoagulants is often effective, but sometimes the diagnosis is missed, and by the time the patient is seen there is chronic oedema of the hand and forearm, which is difficult to relieve. Sympathetic block has been suggested, but I have never seen any benefit follow this procedure in such a case.

Phlegmasia cerulea dolens

This is the syndrome of sudden massive thrombosis of the veins draining the lower limb, which becomes swollen, blue, and painful, and gangrene of venous origin is not uncommon. Anticoagulants seem to have little effect on this condition, and it may even develop in a patient who is on anticoagulants. Conservative management with elevation of the limb and analgesics is usually recommended, but there is probably a case for considering surgical treatment with thrombectomy, as recommended by Haller.[18]

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Drugs and Placental Barrier

Q.—*Is it possible to say in general which drugs cross the placental barrier and which do not?*

A.—In recent years there has been much interest in the passage of drugs and other substances across the placental barrier, and there are a number of excellent reviews dealing with this subject.[1-4] In general terms it can be said that almost any substance can penetrate the placental barrier to some extent, although some drugs are so rapidly destroyed that they do not reach an effective concentration in the maternal blood. When the degree of permeability is low the amount which reaches the foetus is neither pharmacologically active nor physiologically detectable.

It is possible to recognize the passage of drugs through the placenta either by detecting their presence in the foetal blood after administration to the mother or by observing their known pharmacological effects on the foetus. For example, it can be inferred that antithyroid drugs cross the placental barrier because babies born to mothers receiving these drugs have enlarged thyroids. Similarly, oral anticoagulant drugs administered during pregnancy can cause a haemorrhagic state in the foetus. Naturally, most information is available about drugs which are used in obstetrics.

All the commonly used hypnotics, analgesics, narcotics, and anaesthetics cross the placental barrier readily and rapidly. The notable exceptions are the muscle relaxant drugs such as tubocurarine, gallamine, decamethonium, and suxamethonium, which, when administered in the usual doses, apparently do not cross the placenta. In animals, however, it is found that when these drugs are given in large doses they do affect the foetus, so that the placenta is a relative rather than an absolute barrier to their passage. Of other