Mechanisms of deep vein thrombosis: a review[1]

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Spontaneous deep vein thrombosis of the lower limb is a relatively common condition. Most cases arise during the course of another illness in middle-aged or elderly patients confined to bed. Since the time of Virchow, venous stasis has been recognized as the major predisposing factor.

Pathology of spontaneously-arising thrombi

Spontaneously-arising thrombi may be found anywhere in the body, but the great majority arise in the valve pockets and dilated sinuses of the lower limb veins (Sevitt 1959, Sevitt & Gallagher 1961, Patterson 1969). On the basis of detailed histological studies, Sevitt (1970) proposed the scheme of thrombus formation shown in Figure 1. Thrombus begins from a 'nidus' in a valve pocket or saccule. This nidus usually consists of silted red cells, platelet clumps and white cells, held together by fibrin strands. At first, growth is by propagation in the direction of venous stream through deposition of successive layers of fibrin and platelets. With further propagation venous flow may become obstructed and this leads to retrograde thrombosis.

The role of endothelial damage and platelet interactions in the formation of the nidus is unclear. Sevitt (1974) studied 50 recent thrombi in femoral veins and found that virtually all were lying over intact endothelium. Furthermore, the primary thrombi were platelet-free or

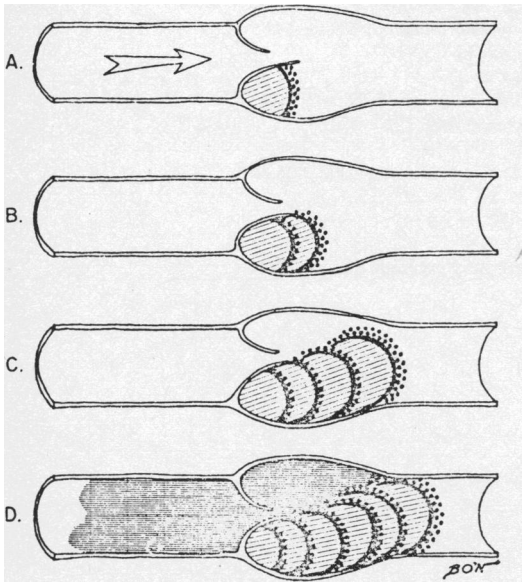

Figure 1. The propagation of deep vein thrombi from a nidus in a valve pocket (A) and the deposition of successive layers of fibrin, platelets, etc. (B, C). Retrograde extension occurs when there is venous blockage from propagation (D). (Reproduced from Sevitt 1970, by kind permission)

[1] Paper read to Section of Medicine, Experimental Medicine & Therapeutics, 28 February 1978. Accepted 17 May 1978

0141–0768/79/080602–04/$01.00/0

platelet-poor, confirming that platelets probably do not play an important role in the formation of the original nidus. To further clarify the nature of the original nidus, Sevitt (1974) then studied macroscopically-empty valve pockets. Of the 35 pockets studied histologically, 13 were not empty microscopically: 7 contained red cells, white cells and fibrin strands, 4 had fibrin strands only, one disclosed a platelet aggregate and one a mass of white cells. Such a small nidus formed in the presence of stasis or turbulent flow is easily washed out, phagocytosed or lysed. It only becomes stable if thrombin is generated to produce anchoring fibrin strands and platelet aggregates. If stasis persists and natural defence mechanisms against spontaneous intravascular thrombosis fail, the thrombus begins to propagate as shown in Figure 1. A large thrombus may be lysed, organized, recanalized or fragmented.

In the healthy human there are many circulatory areas where blood may remain stagnant for a long time without thrombosis. The fluidity of blood in the presence of stasis is ensured by natural defence mechanisms: intact vessel wall, plasma inhibitors, clearance mechanisms and fibrinolysis.

Vessel wall

Intact venous endothelium is absolutely nonthrombogenic. It is a living monolayer of cells which has by evolution become specialized for its role in separating blood from other structures of the vessel wall. The nonthrombogenicity is a property of the intact cell membrane, but there are other mechanisms in the vessel wall which may help in preserving fluidity. Two such systems are the prostacyclin generating system (Moncada *et al.* 1977) and the plasminogen activator release (Nilsson 1974). The first system produces potent antiplatelet-aggregating agents, and the second ensures that any intravascular fibrin is rapidly lysed.

Injury to a blood vessel causes a change in the characteristics of the vessel wall surface that allows platelets to adhere to the injured site and activates the coagulation sequence with the formation of haemostatic plug. The principal mechanisms involved in the formation of plug (Mustard & Packham 1977) are: (1) platelet adherence to the vessel wall; (2) activation of coagulation; (3) release and loss of platelet constituents; (4) formation of thromboxane A_2 and prostaglandin endoperoxides; (5) platelet aggregation and further acceleration of coagulation by the aggregated platelets; (6) fibrin formation.

The injury-induced haemostatic plug may serve as a starting point of massive thrombosis. The best example is perhaps the femoral vein thrombosis after total hip replacement. Stamatakis and his colleagues (1977) have recently shown that a large proportion of such thrombi arise from the wall of the femoral vein at the level of the lesser trochanter, an area where severe distortion of vein and presumed endothelial damage occurs during the operation. The injury-induced thrombi may also precipitate remote thrombosis by releasing partially aggregated platelets or activated clotting factors. Such platelets and coagulation factors are highly thrombogenic (Walsh 1975, Wessler & Yin 1968); they may stabilize potential nidi in the areas of stasis and precipitate clinical venous thrombosis.

It is possible that venous endothelium may lose its nonthrombogenicity in the presence of stasis without overt injury. Stewart (1975) suggested that venous stasis helps in establishing a chemotactic gradient across the endothelium which in turn induces extensive leukocyte migration. The leukocytes that leave the lumen of the vessel become entrapped between the endothelium and the basement membrane. This results in endothelial cell separation and desquamation with exposure of subendothelial layers and subsequent thrombosis. In experimental animals (Stewart 1975) this mechanism has been studied by electron scanning microphotography; it was demonstrated that extensive endothelial damage by leukocytes occurred when venous stasis and tissue injury (such as operation) were present at the same time. Stewart suggested that remote tissue destruction was necessary for triggering the formation and release of chemotactic factors, whereas stasis was essential for establishing the chemotactic gradient across the endothelium.

There are at present no data on the role of this mechanism in human venous thrombosis; it thus remains a fascinating possibility.

Plasma inhibitors of serine proteases

Blood coagulation is kept in check by the neutralization of activated clotting factors as and when they are formed. Human blood contains six well characterized protease inhibitors and four of these, antithrombin III, C-1 inactivator, alpha$_2$-macroglobulin and alpha$_1$-antitrypsin, have an inhibitory action on one or more coagulation factors (Ogston & Bennett 1977).

Antithrombin III is an alpha$_2$-globulin and the main physiological inhibitor of thrombin, factors Xa, 1Xa, X1a and X11a. The inhibition is greatly accelerated and potentiated in the presence of heparin; antithrombin III is the heparin co-factor of plasma. C-1 inactivator is a neuraminoglycoprotein that inactivates the complement pathway, but can also neutralize active forms of factor X1, X11 and plasma kallikrein. Alpha$_1$-antitrypsin is a major trypsin inhibitor of plasma and can also inhibit factor X1a. Alpha$_2$-macroglobulin is a high molecular weight glycoprotein that inhibits the activity of thrombin by forming complexes with it. It accounts for about 25% of the total antithrombin activity of normal plasma.

A predisposition to venous thrombosis has been associated with acquired low antithrombin III levels, as after surgery and during oestrogen treatment (Fagerhol & Abildgaard 1970, Meade *et al.* 1976, Sagar *et al.* 1976). The hereditary deficiency or defect of antithrombin III is associated with major thromboembolic disease starting in adolescence or during the first pregnancy in women (Mackie *et al.* 1978). The prompt neutralization of activated clotting factors is obviously of major importance in preventing stasis-induced thrombosis.

Clearance mechanisms

Activated clotting factors and platelets are cleared from the circulation by the liver and the reticuloendothelial system (Hirsh 1977). In areas of stasis, the potentially thrombogenic material cannot be washed away to reach the usual site of clearance. When local defences against thrombin generation and permanent fibrin deposition are exhausted, activated clotting factors and platelets can initiate thrombus formation or induce growth of already existing thrombi.

Fibrinolysis

Fibrinolysis is the enzyme system responsible for degradation of fibrin clots. The four components of this system are plasminogen, plasmin, inhibitors and plasminogen activators (Kernoff & McNicol 1977).

Plasminogen is a beta-globulin present in normal plasma. In the presence of activators it is cleaved into plasmin, a serine protease that breaks fibrin strands into fibrin degradation products.

Inhibitors are of two main types: antiactivators and antiplasmins. Antiactivators are alpha$_2$-globulins; the major antiplasmins are alpha$_2$-macroglobulins, alpha$_1$-antitrypsin, and the fast reacting antiplasmin (Edy *et al.* 1976).

Plasminogen activators are present in blood, tissue and body fluids. The blood activator is derived from the vascular endothelium. It is released rapidly after venous occlusion, strenuous exercise and administration of vasoactive drugs.

The activator activity of the arm veins is 3–4 times as high as that in the legs, as measured after venous occlusion or in biopsy specimens (Nilsson 1974). Veins containing fresh obstructing thrombi have little or no activity. The blood and vessel wall activator activity is low in patients with recurrent deep venous thrombosis, postoperatively and after myocardial infarction (Nilsson 1974, Clayton *et al.* 1976). These observations suggest that a decreased content of activators of fibrinolysis or impaired release are an important predisposing factor in venous thrombosis.

Hypercoagulability

Hypercoagulability is a term used to describe the changes in blood that may predispose to thrombosis. The changes are an increase in procoagulants, including clotting factors and

platelets, or a decrease in the factors that prevent thrombosis, such as plasma inhibitors and fibrinolytic activity.

The increase in clotting factor concentration is a part of the physiological response to trauma or illness, the acute phase reaction (Hirsh 1977, Brozović 1977). Although the rise in plasma levels of fibrinogen, factor VIII and factor V found in acute phase reaction does not induce thrombosis *per se*, it favours thrombosis through increased blood viscosity and increased concentration of factors essential in coagulation sequence and fibrin formation.

Trauma and operation are also associated with the reduction in plasma antithrombin III levels and plasminogen activation activity (Brozović 1977). Again, this does not initiate thrombus formation, but may contribute to its formation in the presence of stasis and other predisposing factors.

Conclusions

Most individuals for most of the time are remarkably resistant to spontaneous venous thrombosis. In the presence of stasis the fluidity of blood is maintained by intact endothelium, abundant plasma inhibitors and vigorous fibrinolysis. When the last two mechanisms fail, the thrombus can be formed even over the intact endothelium from silted cells and locally-deposited fibrin. The growth and formation of thrombi are facilitated in the presence of damaged endothelium, activated clotting factors or platelets. Spontaneous venous thrombosis occurs as a result of local failure to maintain blood fluidity, and in most instances more than one contributing factor is present.

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