VENOUS THROMBOEMBOLISM

Epidemiology and Pathogenesis of Venous Thrombosis

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Venous thrombi are intravascular deposits composed predominantly of fibrin and red blood cells with a variable platelet and leukocyte component. They frequently arise in large venous sinuses in the calf, in valve cusp pockets either in the deep veins of the calf or thigh or in venous segments that have been exposed to direct trauma. Venous thrombosis can be produced experimentally by a combination of stasis and systemic hypercoagulability or by stasis and endothelial damage. Thrombosis is augmented if the fibrinolytic mechanism is inhibited or defective. A number of clinical conditions and laboratory abnormalities are associated with and predispose to venous thrombosis and, in many of these, it is possible to identify one or more of the thrombogenic factors discussed.

Venous thromboembolism (venous thrombosis and pulmonary embolism) is a serious and potentially fatal disorder that usually complicates the course of sick hospitalized patients, but occasionally affects ambulant and otherwise healthy individuals. Screening studies with iodine-125 fibrinogen leg scanning, impedance plethysmography and perfusion lung scanning have shown that the majority of venous thrombi and pulmonary emboli that occur in hospitalized patients are small and asymptomatic, and it is likely that most are clinically insignificant. In bedridden patients, most thrombi commence in the calf and are asymptomatic. When a calf vein thrombus extends into the proximal venous segment, the risk of clinically significant pulmonary embolism increases. Less is known about the incidence and clinical significance in a nonhospital population; although asymptomatic disease occurs, its frequency is unknown. In contrast to the patients with asymptomatic venous thrombosis, symptomatic patients with venous thrombosis usually have large occlusive thrombi localized in their proximal veins.

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Epidemiology

Venous thrombosis can involve the superficial leg veins, deep veins of the calf (calf vein thrombosis) and deep veins above the knee (popliteal and more proximal veins [proximal vein thrombosis]). Thrombosis of the superficial veins of the legs frequently occurs in varicosities and is usually benign and self-limiting. Thrombosis of the deep calf vein is a less serious disorder than proximal vein thrombosis because the thrombi are generally smaller in patients with calf vein thrombosis and are less frequently associated with clinical disability or major complications.

Incidence. Deep venous thrombosis and pulmonary embolism usually complicate the course of sick hospitalized patients, but it is clear from recent studies (1–4) that venous thromboembolism also affects ambulant and otherwise healthy individuals. Over the last decade, screening studies (5) with iodine-125 fibrinogen leg scanning have shown that venous thrombosis is common in hospitalized patients, but that more than 80% of the thrombi detected are small, asymptomatic, confined to the calf and probably clinically insignificant. Autopsy studies (6) have also demonstrated a high frequency of pulmonary embolism, which although the majority are small and clinically insignificant, the fact remains that fatal pulmonary embolism is one of the most common preventable causes of hospital death. Fatal pulmonary embolism has been reported (7,8) in 4 to 7% of patients after emergency hip surgery, in 0.3 to 1.7% of patients after elective hip replacement and 0.1 to 0.8% of general surgical patients. The frequency and distribution of venous thromboembolism in ambulatory patients has been much more difficult to study. However, as mentioned, recent experience since the provision of a noninvasive diagnostic service indicates that venous thrombosis is not uncommon in ambulant non-
hospitalized patients. When patients with venous thrombosis develop symptoms, they usually have large occlusive thrombi, and approximately 80% of these are either located or extend into the popliteal or more proximal veins at the time of presentation (3,9). Symptomatic pulmonary embolism occurs in ambulant patients (3) more frequently than is generally appreciated, but fatal pulmonary embolism is uncommon.

Fate of venous thrombosis. When symptoms or signs of venous thrombosis occur, they are caused either by obstruction to venous outflow, inflammation of vessel wall or perivascular tissue, a combination of these two factors or embolization of the thrombus into the pulmonary circulation. The fate of a venous thrombus is determined by the balance between factors that either promote further deposition of fibrin onto the thrombus or that lead to its removal. Extension of thrombosis is more likely to occur if the original thrombogenic stimulus persists (for example, tissue injury, stasis or vascular damage) or if marked endothelial damage or stasis occurs as a consequence of the original acute venous thrombosis. The factors that lead to the removal of thromb i are fibrinolysis, digestion of fibrin by leukocytes, organization of the thrombus and embolization. Complete spontaneous lysis of large venous thrombi is uncommon and, even when patients with venous thrombosis are treated with heparin, complete lysis occurs in less than 10% of cases (10,11). In contrast, complete dissolution of small, asymptomatic calf vein thrombi (detected by iodine-125 fibrinogen leg scanning) occurs quite frequently (5).

Pulmonary embolism is commonly associated with venous thrombosis. Clinically silent pulmonary embolism (detected by perfusion lung scanning) occurs at the time of presentation in about 50% of patients with documented vein thrombosis (12,13). Pulmonary emboli occur more frequently and are larger in patients with proximal vein thrombosis than in patients with calf vein thrombosis (3).

Asymptomatic venous thrombosis is also found in approximately 70% of patients who present with confirmed clinically symptomatic pulmonary embolism (3) and is usually extensive, involving the proximal veins. If the thrombus that embolizes is small (which is frequently the case when it is present in the calf), the embolus is usually asymptomatic and clinically insignificant (12). However, if it is large and involves the proximal veins, it may produce clinical manifestations (3) and, if it is very large or if the patient has a compromised cardiorespiratory system, it may be fatal. Most clinically significant and fatal emboli arise from thrombi in the proximal veins of the leg (2).

Venous thrombi usually slowly organize and recanalize and may predispose patients to the postphlebitic syndrome because of associated venous valve damage (14). In addition, patients with one episode of venous thrombosis are predisposed to further episodes when exposed to high risk situations (15,16).

Pathogenesis of Venous Thromboembolism

Venous thrombi are composed predominantly of fibrin and red blood cells with a variable platelet and leukocyte component (17). They frequently arise in large venous sinuses in the calf, in valve cusp pockets either in the deep veins of the calf or thigh (18,19) or in venous segments that have been exposed to direct trauma (20,21).

Experimental venous thrombosis can be produced by a combination of stasis and an increase in blood coagulability or by a combination of stasis and endothelial damage (22,23).

Predisposing factors. Clinically, the major predisposing factors to venous thrombosis are activation of blood coagulation, venous stasis and vascular wall damage (21,22,24). These three factors are interrelated and, thus, venous thrombosis may occur when blood coagulation is activated by the release of tissue thromboplastin from injured or infarcted tissue (25–27) or when blood coagulation is activated locally by vessel wall damage (20,24). The thrombogenic effect of activation of blood coagulation is augmented by venous stasis and reduced by rapid blood flow. For example, as discussed later, one of the reasons is that venous stasis impairs the clearance of activated coagulation factors by the liver and results in an increase in the concentration of activated coagulation factors through the autocatalytic activity of the coagulation system (22,28).

Thrombogenic Factors

Activation of Blood Coagulation

The coagulation proteins circulate as proenzymes that are sequentially converted to active enzymes, all of which are serine proteases (28). The blood coagulation process can be activated by the intrinsic or extrinsic pathway (36), and this has been reviewed in the first section of this symposium. In brief, intrinsic pathway activation occurs when blood comes in contact with a foreign surface (37). Factor XII interacts with the surface and is converted into its active form—factor XIIa. This, in turn, converts the zymogen factor XI into factor Xla, a reaction that is calcium-independent; all subsequent reactions except the conversion of fibrinogen to fibrin require calcium. Factor Xla, in turn, activates factors IX and IIXa in the presence of factor VIII, and phospholipid activates factor X. The rate of this reaction is greatly increased by the presence of phospholipid and by prior exposure of factor VIII to either thrombin or factor Xa (38,39).
The extrinsic pathway is activated in vitro by exposing blood to phospholipoprotein extracts from various tissues (such as brain or lung), which are known as thromboplastins. Tissue thromboplastin combines with and activates factor VII and the resulting factor VII complex, in turn, activates factor X, thus bypassing a number of time-consuming steps in the intrinsic clotting pathway (40,41).

The intrinsic and extrinsic pathways meet at a common point at the activation of factor X; beyond this point, blood coagulation continues along a common pathway. Activated factor X in the presence of calcium, phospholipid and factor V converts prothrombin to thrombin. This reaction is also markedly accelerated by prior exposure of factor V to thrombin. Thrombin interacts with fibrinogen and converts it into fibrin monomer and fibrinopeptides A and B. The fibrin monomer fragments polymerize to form fibrin polymers, which precipitate as insoluble fibrin when a critical concentration of fibrin monomer is reached (42). The fibrin polymers are initially linked by noncovalent bonds, but become covalently bound under the influence of activated factor XIII (43).

Interactions between intrinsic and extrinsic pathways. Blood coagulation is modified by a number of positive and negative feedback loops and by interaction between the intrinsic and extrinsic pathways. For example, thrombin and factor Xa, formed either by activation of the extrinsic or intrinsic pathway, feed back to activate factors VIII and V and markedly accelerate the rate of reactions involving these two cofactors (36,39,44). Factor Xa feeds back to initially increase and then inhibit its activation by factor VII (41,45). The intrinsic and extrinsic pathways are linked in a number of ways. Factor VII is activated by factor XIIa (46), and factor VIIa can activate factor IX directly (44,45,47). There is also evidence that the activation of factor XI can occur independently of factor XII through a platelet-related reaction (48).

Mechanisms for activation of venous blood coagulation. The precise mechanism or mechanisms for activation of blood coagulation, particularly for the venous system, is uncertain. There are a number of theoretic possibilities. Activation of the intrinsic pathway may occur by contact of factor XII with collagen on the exposed subendothelium of damaged vessels (49,50). Coagulation may be further augmented through a platelet-related mechanism because platelets that have been exposed to collagen or adenosine diphosphate (ADP) accelerate the activation of factors XII and XI (48). The extrinsic pathway may be activated by the release of tissue thromboplastin into the bloodstream during cell damage (25,27) and by the exposure of blood to tissue thromboplastin, which is made available locally as a result of vascular wall damage (51) and by activated leukocytes that migrate to areas of vascular damage (52,53). Factor X can be activated directly by extracts of malignant cells that contain a cysteine protease (54), and this may be one of the mechanisms by which thrombosis is induced in patients with malignant disease.

A number of clinical risk factors could induce venous thromboembolism by activating blood coagulation (21). These include extensive surgery (55), trauma (56), burns (56), infusion of factors II, VII and IX and X complex (for the treatment of bleeding associated with factor IX deficiency or liver disease) which contain activated clotting factors, (57) disseminated malignant disease (54,57) and myocardial infarction (26).

Venous Stasis

Stasis predisposes to venous thrombosis by preventing activated coagulation factors from being diluted by nonactivated blood, preventing clearance of activated coagulation factors, and preventing mixing of activated coagulation factors with their inhibitors (21,22).

Physiologically, venous return from the legs is enhanced by contraction of calf muscles, which propels blood from the calf in the direction of the heart (59–61). Venous stasis is produced by immobility, venous obstruction, raised venous pressure, increased blood viscosity and venous dilation.

Immobility. This predisposes to venous stasis and, therefore, thrombosis because it promotes blood pooling in the intramuscular sinuses of the calf (18,59,61), which are dilated with blood during recumbency (15,19). Thus, the prevalence of venous thrombosis found at autopsy increases steeply in patients who are confined to bed for more than 1 week before death (59). Preoperative immobility is also associated with a higher frequency of preoperative venous thrombosis (62,63). Postoperative patients remain at risk during the entire period of immobility, and late postoperative thrombosis is not prevented in patients who have prophylaxis in the first postoperative week (either with low dose heparin or with intermittent pneumatic compression) if they remain immobile beyond the period of prophylaxis (64,65). Immobility contributes to the higher incidence of postoperative venous thrombosis in patients who undergo hysterectomy or prostatectomy using the abdominal route than in those who have vaginal hysterectomy and transurethral prostatectomy (15,66–70). Immobility also contributes to the high frequency of thrombosis after hip surgery (20, 70–73) and knee surgery (74,75) and in patients who have fractures of the lower limb.

The effect of immobility on thrombosis is well illustrated by comparing the location of thrombosis in stroke patients (76,77) with that in paraplegic patients (78). Venous thrombosis is a common complication in both groups, but the frequency of thrombosis is four to nine times greater in the paralyzed than in the nonaffected limb in patients with stroke;
it occurs with equal frequency in both legs in paraplegic patients (76,78). Immobility also contributes to the high prevalence of thrombus in patients with cardiac failure and other serious medical illnesses.

Venous obstruction. This may occur as a result of either extrinsic compression or intraluminal obstruction secondary to a previous venous thrombosis. Stasis produced by venous obstruction probably contributes to the risk of venous thrombosis in patients with pelvic tumor and to recurrent venous thrombosis in patients with persistent obstruction due to proximal vein thrombosis (79).

Elevated venous pressure. This produces venous stasis and predisposes to the high prevalence of venous thrombosis in patients with heart failure (80,81).

Blood viscosity. Blood flow and blood viscosity are closely linked (82). Blood viscosity increases in regions of slow flow. However, blood viscosity is increased in polycythemia vera and erythrocytosis (because of hypergammaglobulinemia) and in some postoperative patients and inflammatory states (because of an increase in fibrinogen concentration) (83,84). It is possible that the increased prevalence of venous thrombosis in these conditions is caused by stasis induced by an increase in blood viscosity.

Venous dilation. This occurs in patients with varicose veins and in elderly patients (particularly if they are bedridden), during pregnancy (85) and in individuals taking estrogen-containing oral contraceptive pills (85). Stasis due to venous dilation could contribute to the increased risk of thrombosis in these patient groups.

Vessel Wall Damage

As discussed, damage to the venous endothelium results in the exposure of blood to subendothelium, which in turn leads to platelet adhesion and aggregation (23,86), local accumulation of leukocytes (53), activation of the intrinsic pathway through activation of factor XII by collagen (49) and activation of factors XII and XI by activated platelets (48). Activation of the extrinsic pathway also occurs by tissue thromboplastin derived from the damaged vessel wall (51) and activated leukocytes (87).

Venous damage is probably the main contributor to venous thrombosis in patients undergoing hip surgery (20), knee surgery and varicose vein stripping in patients with severe burns and lower limb trauma (56).

Protective Mechanisms

These mechanisms will be described in more detail than in previous sections since their preventive role in venous thromboembolic disease is better known. On the other hand, a decrease or absence of one of these protective mechanisms may predispose to venous thrombosis.

Circulating Inhibitors

Three plasma proteins have been identified as important modulators of activation of blood coagulation. These are antithrombin III, protein C and protein S.

Antithrombin III. This is an important coagulation inhibitor (30,31,88). It inhibits activated factors XII, XI, IX, X and thrombin (although inhibition of factors XIIa and Xla is relatively minor), and the rate of its inhibition of these enzymes is markedly increased by heparin (30,31).

Reduction of antithrombin III levels to approximately 50% of normal predisposes to venous thrombosis (89–94). Although antithrombin III is a relatively slow inactivator of these activated clotting factors in the absence of heparin, a heparin-like glycosaminoglycan has been reported (95,96) on the luminal surface of endothelial cells, so that a 50% reduction in antithrombin III might seriously limit the neutralization of activated coagulation factors on endothelial surface.

Thrombin binds to receptors on the endothelial cell surface, where it is inactivated by circulating antithrombin III. One of these receptors is thrombomodulin, and others may be glycosaminoglycan bound to endothelium. Thrombin bound to endothelium is rapidly inactivated in the presence of plasma, but only slowly if the plasma is replaced by either antithrombin III or antithrombin III-depleted plasma. Thus, potentiation of the inhibition of endothelial cell-bound thrombin by glycosaminoglycan appears to be dependent on the presence not only of antithrombin III, but also of an additional plasma factor.

There have been a number of reports (89–94) of idiopathic and secondary venous thrombosis occurring in families with a deficiency of antithrombin III. The trait is inherited in an autosomal dominant manner, and affected patients have antithrombin III levels of 40 to 60% of normal. Although it is difficult to obtain exact figures on the risk of thrombosis in affected individuals because of the likelihood of a reporting bias, review of the literature indicates that more than 50% of affected individuals develop thromboembolic events before the age of 50 years. Thrombosis usually occurs in the deep veins of the legs or as a pulmonary embolism, but there are reports (84) of thrombosis occurring in usual sites such as the mesenteric veins.

Decreased antithrombin III levels also occur in liver disease and during heparin therapy. In patients with liver disease, this decrease may contribute to the increased risk of thrombosis that has been reported (97) in these patients after infusions of concentrates containing factors II, VII, IX and X. There is no evidence that the mild reduction in antithrombin III that occurs during heparin therapy is clinically important.

Protein C. This is a zymogen whose synthesis is vitamin K-dependent (98). Like other vitamin K-dependent coag-
ulation factors, protein C contains a number of gamma-carboxyglutamic acid residues (99). The amino acid sequence of bovine protein C has recently been determined (100).

**Protein C is activated by thrombin** (29). The activation process is greatly enhanced by interaction of thrombin with the endothelial cell surface factor thrombomodulin (101). Activated protein C is a potent anticoagulant (102) that inactivates activated factors V and VIII and also stimulates fibrinolysis (32,103). Walker (104) reported that another vitamin K-dependent protein (protein S) is a cofactor for activated protein C. (104).

**Deficiency of protein C is associated with familial venous thrombosis** (105–107). Protein C deficiency is also inherited in an autosomal dominant manner. The level of protein C in affected members is 40 to 60% of normal, similar to that seen in patients with antithrombin III deficiency. Most patients have venous thromboembolism. Mesenteric vein thrombosis has also been described, and there have been isolated reports of stroke and myocardial infarction occurring at a relatively early age. However, there is no convincing evidence that protein C predisposes to arterial thrombosis.

**Protein S**. This is a vitamin K-dependent plasma protein that is a cofactor for activated protein C and is required for the expression of the anticoagulant effect of protein C (108–110). Despite its relatively recent discovery, protein S deficiency has already been reported (108,111–114) in more than 50 patients with recurrent venous thrombosis. Venous thromboembolism is often idiopathic, may be familial and frequently occurs before the age of 30 years. The clinical disorder affects both sexes equally, and is expressed in heterozygotes whose levels of functional protein S are in the range of 15 to 50% of normal (108,111). Preliminary reports suggest that patients can be treated effectively with long-term oral anticoagulant therapy.

**Heparin cofactor II**. This is a plasma protein that inhibits thrombin activity by forming a covalent complex with the enzyme. The formation of the complex is catalyzed by heparin and dermatan sulfate. There have been two reports of thrombosis associated with heparin cofactor deficiency, but a definite causal relation has not been established (115).

**Hepatic Inactivation of Activated Coagulation Factors**

The liver removes activated coagulation factors from blood (33). Thrombosis has been reported in patients with liver disease after the infusion of concentrates of factors II, VII, IX and X (57). These concentrates contain a small amount of activated coagulation factors, which may not be adequately cleared in patients with liver disease and, thus, lead to thrombosis (57,116,117).

**Fibrinolytic System**

The basic reaction of the plasma fibrinolytic system is the conversion of beta-globulin plasminogen to plasmin by proteolytic cleavage mediated by a number of plasminogen activators (35,118). At least two plasminogen activators, tissue plasminogen activator and urokinase, are synthesized by and released from endothelial cells. Plasmin has the capacity to hydrolyze fibrin (the desired physiologic substrate) and various plasma coagulation proteins including fibrinogen and factors VII and V (35). Like the coagulation system, the activity of the fibrinolytic system is modulated by inhibitors that inhibit both the activation of plasminogen and the proteolytic effect of plasmin (35,119).

**Decreased fibrinolytic activity.** This has been reported in patients in the early postoperative period (120–124), in individuals taking oral contraceptives (125), during the last trimester of pregnancy (126–128) and in obese individuals (62,128,130). Fibrinolytic activity has been found to be less in leg veins than in arm veins (131,132), an observation that may explain, in part, the greater tendency for venous thrombosis to occur in leg veins. The relative deficiency of fibrinolytic activity in leg veins appears to be more marked in the elderly (132), which may explain, in part, the importance of old age as a risk factor in thrombosis. An association between defective fibrinolysis and postoperative thrombosis has been observed when fibrinolytic activity is measured preoperatively and on the first postoperative day (120–124). Postoperative venous thrombosis has been reported to occur more frequently in patients who have reduced fibrinolytic activity detected either as a high antiplasmin level or as reduced plasminogen activator level (120–124).

**Relation between reduced fibrinolytic activity and recurrent venous thromboembolism.** There have been a number of reports (132–135) that patients with recurrent superficial and deep vein thrombosis have reduced fibrinolytic activity measured either as vessel wall plasminogen activator (from biopsy specimens of superficial veins) or as circulating plasminogen activator. In uncontrolled studies (133,136), treatment of some of these patients with anabolic steroids has been reported to both increase fibrinolytic activity and reduce the frequency of recurrent venous thrombosis (136,137).

Recurrent venous thrombosis and pulmonary embolism has been reported in a patient who had decreased levels of plasminogen when measured immunologically (138). Other members of the patient’s family also had a reduced ratio of functional to immunologic plasminogen, but did not have a history of thrombosis. Further evidence for a relation
between reduced fibrinolytic activity and thrombosis comes from a report (138) of high antiplasmin levels occurring in a family with idiopathic pulmonary hypertension.

Clinical Risk Factors and Their Relation to Thrombogenesis

Surgery and trauma. A number of well recognized thrombogenic factors are associated with surgery and trauma. These include 1) increased blood coagulability due to release of tissue thromboplastin into the blood (25,27); 2) stasis due to immobilization preoperatively, during operation and during the postoperative period and in patients with a plaster cast (59–63); and 3) reduced fibrinolytic activity, which occurs in many patients within 24 hours of surgery (119,123,124). In addition, surgery or trauma to the lower limb may produce local vessel damage (20).

The risk of thromboembolism after surgery is related to the site and extent of surgical trauma as well as to duration and nature of the operative procedure and the length of time that the patient remains immobilized preoperatively and postoperatively (15,62,140). Orthopedic surgical procedures of the lower limb and trauma to the pelvis and lower limb carry a particularly high risk. Approximately 20% of thrombi in patients who have hip surgery are localized to the femoral vein close to the site of surgery (20,71,141). Operative venography has demonstrated that the femoral vein is markedly twisted and distorted during total hip replacement; it is likely that endothelial damage occurs as a consequence of this manipulation and is responsible for the unique localization of thrombi in the proximal venous segment (20). It is of interest that more than 90% of femoral vein thrombi occur on the side of operation, although calf vein thrombi tend to be evenly distributed in both legs (20,71,141). Patients having major knee surgery or who have sustained tibial fractures requiring cast immobilization are also at very high risk of venous thrombosis (55).

Examples of the important role of surgical trauma and immobilization in the risk of thrombosis are provided by comparing the thrombosis rate for abdominal hysterectomy with that for vaginal hysterectomy (69) and by comparing suprapubic prostatectomy with transurethral prostatectomy (65–67). The risk of thrombosis is much higher when these procedures are performed by an abdominal approach.

Age. Age is a very important risk factor for venous thrombosis, but the underlying mechanism is uncertain (15,62). Venous dilation occurs in the elderly, particularly when they are confined to bed, and in addition to their greatly reduced mobility, results in venous stasis. The fibrinolytic response to venous occlusion of the legs is reported to be significantly lower in persons older than 65 years of age than in those younger (132). These older people have less releasable activator in endothelial cells. Other unknown mechanisms also probably contribute to the very high risk of venous thrombosis that occurs with advanced age.

Malignancy. Patients with malignant disease may develop recurrent superficial deep vein thrombosis, thrombosis in unusual sites and, rarely, thrombosis that is resistant to anticoagulant therapy. The frequency of postoperative venous thrombosis increases two- to threefold in patients undergoing surgery for malignant disease when compared with similar surgical procedures for nonmalignant conditions (15,55,62). However, the extent of surgery could be greater in patients with malignant disease, so that the effect of malignancy as an independent risk factor for thrombosis is difficult to determine in these postoperative patients (142).

A number of factors could contribute to the increased risk of venous thrombosis in patients with malignant disease. Material that has both tissue thromboplastin-like activity and factor X-activating activity has been isolated from malignant tissues (54,58), and patients with cancer have been reported to have reduced fibrinolytic activity (143). Malignant tumors may either compress or infiltrate veins and so predispose to thrombosis. Patients with malignant disease have associated confounding risk factors in that they tend to be older and, as mentioned, require more extensive and prolonged surgery than those with benign disease.

Heart failure. Heart failure is a well recognized risk factor for venous thromboembolism, and pulmonary embolism is an important cause of death in patients with heart failure (21,81). The increased risk of venous thrombosis in these patients is contributed to by increased central venous pressure and mobility, both of which lead to venous stasis.

Previous venous thromboembolism. Patients with a history of previous venous thrombosis have a three- to fourfold increased risk of developing venous thrombosis after elective abdominal surgery than do patients without such a history (15,62). In addition, the rate of recurrent venous thrombosis is three- to fourfold greater when anticoagulant therapy is discontinued after 3 months in patients with recurrent venous thrombosis than in patients who have only one episode of venous thrombosis (79). The increased risk of thrombosis in patients who have had an episode of venous thrombosis may be caused by venous stasis, which occurs as a consequence of valve damage, or by venous obstruction or alterations in the blood (either recognized, for example, deficiency of antithrombin III, protein C, protein S, plasminogen or possibly heparin cofactor II, or unrecognized), which predisposed the patient to the initial episode.

Obesity. A number of studies (15,62) have reported that obesity is associated with an increased risk of postoperative thrombosis. Obesity has been reported to be associated with impaired fibrinolytic activity; in addition, obese patients (129,130) are more likely to remain immobile for longer...
Periods of time after operation than are their nonobese counterparts.

**Pregnancy and the pill.** Pregnancy and the estrogen-containing oral contraceptive pills are recognized as risk factors for venous thrombosis. However, evidence supporting pregnancy as a risk factor is imperfect, and there is no good evidence that the "low dose" estrogen-containing pill is a risk factor for venous thrombosis.

*A number of thrombogenic factors operate during normal pregnancy and delivery.* These include a decrease in fibrinolytic activity, which occurs in the third trimester (126–128) and in the early stages of labor before placental separation (127), release of tissue thromboplastin into the circulation at the time of placental separation (126), venous stasis, which occurs as a result of deep venous dilation (85), and pressure of the uterus during the third trimester of pregnancy and during delivery. There is also an increased level of plasma fibrinogen and coagulation factors VII, VIII, and IX during pregnancy, but these are unlikely to contribute to the risk of thrombosis (126). Estrogens in oral contraceptive pills produce many of the changes that occur in pregnancy. They produce venous dilation (85) and, in some studies, estrogens have been reported to decrease functional levels of antithrombin III (144) and decrease fibrinolytic activity (125). Estrogen also causes elevations in the level of a number of coagulation factors, but this is unlikely to be important in thrombogenesis (145,146).

**Other clinical disorders that predispose to venous thromboembolism.** Other conditions that have been reported to be associated with venous thromboembolism include thrombocytosis, polycythemia vera and systemic lupus erythematosus. When thrombocytosis occurs after splenectomy or other surgical procedures, it is transient and not associated with an increased risk of venous thrombosis (147,148). In contrast, thrombocytosis associated with myeloproliferative disorders such as polycythemia vera (149) or with splenectomy in patients with sideroblastic anemia and other hemolytic anemias has been reported to be associated with an increased frequency of venous thromboembolism (147). The mechanism of this increased tendency for thrombosis is uncertain, but may be due to the effect of hyperactive platelets. Patients with polycythemia vera have the additional risk factor of high blood viscosity, which also occurs in patients with erythrocytosis due to chronic anoxia.

**Patients with systemic lupus erythematosus** may have recurrent episodes of superficial deep vein thrombosis (150). Recently, immune complexes directed against endothelial cells have been described in patients with systemic lupus erythematosus predisposed to venous thrombosis (150). The presence of lupus-like anticoagulants in patients with systemic lupus erythematosus or in otherwise normal individuals has been reported to be associated with venous thrombosis.

**References**


