

Thrombotic risk factors: Basic pathophysiology

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Although venous thrombosis has been traditionally associated with stasis and hypercoagulability, arterial thrombosis is mainly associated with heightened platelet reactivity and damage to the vessel wall. Accordingly, classic risk factors for venous and arterial thrombosis are usually considered distinct. Those for the former include cancer, surgery, pregnancy, and estrogens use, whereas risk factors of arterial thrombosis include smoking, hypertension, diabetes, the metabolic syndrome, and hyperlipidemia. However, a number of studies have recently challenged this

dichotomy, and it is now recognized that venous and arterial thromboses share several risk factors, suggesting a closer link between the two clinical conditions. Typical examples of shared risk factors are age and the metabolic syndrome. This review addresses the mechanism whereby established risk factors increase the risk of venous or arterial thrombosis, or both. (*Crit Care Med* 2010; 38[Suppl.]:S3–S9)

KEY WORDS: venous thrombosis; arterial thrombosis; risk factors; coagulation; pathogenesis

Although venous thromboembolism is a common disease, underlying pathogenic mechanisms are only partially known, particularly in comparison to those of atherothrombosis. During the past decades, progress has been made in the identification and characterization of the cellular and molecular mechanisms that interdependently influence Virchow's triad. It is now accepted that the combination of stasis and hypercoagulability, much more than endothelial damage and activation, are crucial for the occurrence of venous thrombosis; venous thrombi are mainly constituted by fibrin and red blood cell, and less by platelets. In contrast, platelets are essential for primary hemostasis, repair of damaged endothelium, and play a pivotal role in the development of atherosclerosis. Inflammation, lipids, and the immune system, through a complex interplay, are also important determinants of arterial and venous thrombosis, albeit to a lesser extent. This review considers the various risk factors for venous thrombosis and atherothrombosis, with the goal of de-

scribing the mechanisms by which they mediate disease. These considerations may prove useful when considering the thrombotic risk for patients admitted to the ICU.

Age

The process of aging in humans is accompanied by modifications of the blood coagulation system that explain the heightened risk of thrombosis in the elderly. The plasma concentrations of some coagulation factors (factor V, factor VII, factor VIII, factor IX, fibrinogen) increase progressively with age (1, 2). The same is true for von Willebrand factor, a key protein in platelet–vessel wall interactions (3). For instance, the Framingham study (4) has shown that plasma levels of fibrinogen increase from a mean value of 280 mg/dL in individuals aged 47 to 54 yrs to >300 mg/dL in those aged 65 to 79 yrs, with an increase of 10 mg/dL for each age decade. High plasma levels of fibrinogen may play a causative role in the high incidence of cardiovascular events observed in elderly people, perhaps by enhancing the bridging of platelets via their glycoprotein IIb-IIIa receptor, by serving as a direct substrate of the clot, and/or by increasing blood viscosity (5). Alternatively, high fibrinogen levels simply may be a marker of the chronic inflammatory state typical of aging, without directly contributing to the risk (5). A similar trend was shown for another acute phase protein, coagulation factor VIII, which progressively increases with age, up to >200 U/dL in the seventh decade of life (6). Coagulation factor VII also increases

with age, both as zymogen and activated protease (7). The role of tissue factor and factor VII as key components of blood coagulation and thrombus formation is well-established (Fig. 1). Tissue factor, a protein normally localized to the membrane of vascular cells, monocytes, and circulating microparticles, is considered a key initiator of blood coagulation. When it is exposed in its active form at the vessel wall (e.g., after endothelial activation or during chronic inflammation, both conditions typical of aging), tissue factor activates factor VII. This complex produces small amounts of thrombin and promotes thrombus formation through the activation of coagulation reactions on the membrane surfaces of activated platelets and microparticles (8). During aging, an increasing number of individuals have a laboratory picture of enhanced activity of coagulation enzymes, as expressed by high levels of the activation peptides that are cleaved from prothrombin (prothrombin fragment 1 + 2), factor IX (factor IX activation peptide), factor X (factor X activation peptide), and fibrinogen (fibrinopeptide A) or the presence of activation-dependent complexes (thrombin–antithrombin complex) produced when these zymogens are converted into their corresponding active enzymes (9, 10).

An impairment of fibrinolytic activity occurs with aging. There is an increase of plasminogen activator inhibitor type 1 (PAI-1), the major inhibitor of fibrinolysis (11), and a corresponding age-dependent decrease in fibrinolytic activity (12).

An increase in platelet reactivity with aging has been established, and activated

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platelets greatly accelerate thrombin generation. Platelets of individuals 60 yrs or older aggregate more in response to adenosine diphosphate and collagen than do platelets from younger individuals (13). Furthermore, a positive correlation has been observed between age and such markers of platelet activation as plasma β -thromboglobulin (a protein stored in

platelets α -granules) and platelet membrane phospholipids (14).

Because the vascular endothelium plays an important role in the normal process of hemostasis, any structural or functional change in the vascular wall (involving the extracellular matrix, vascular smooth muscle, or endothelium) that occurs during aging may contribute

to the increased risk of thrombosis in the elderly, particularly of atherothrombosis. Advanced age is characterized by stiffness and dilation of the arteries, attributable to degeneration of elastic fibers and an increase in collagen and calcium content, and by a decrease in prostacyclin and nitric oxide, with a related reduction in the endothelium-dependent dilation (15). There is also increased binding to arteries of platelet-derived growth factor, caused by changes in the glycosaminoglycan content of the vessel wall, that enhances the progression of atherosclerosis and indirectly contributes to atherothrombosis (16).

Thrombophilia

Normally, the coagulation process is under control of several inhibitors that limit clot formation near the damaged vessel wall, thus avoiding thrombus propagation (Fig. 2). This delicate balance can be interrupted whenever an increased procoagulant activity of one of the coagulation factors or a decreased activity of one of the naturally occurring inhibitors takes place, leading to thrombus formation (Table 1). This occurs with inherited deficiencies of natural inhibitors, as well as with inherited gain-of-function mutations of some coagulation factors (17). Antithrombin, protein C and protein S deficiencies are rare but strong risk factors for venous thrombosis; they have little or no effect on arterial thrombosis. Antithrombin directly inhibits several activated coagulation factors, particularly thrombin and activated factor X, and the inhibitory effect is amplified by its binding to glycosaminoglycans of the endothelial surface that carry heparin-like activity. Antithrombin deficiency results in significantly reduced inhibition of thrombin and activated factor X and an increased tendency to clot formation, particularly in the venous system, where the coagulation pathway (as distinct from platelets) plays a more important role in thrombus formation (17). The protein C anticoagulant pathway, localized on the surface of the endothelium, plays an important role in the down-regulation of thrombin generation. Thrombin activates protein C, the presence of thrombomodulin, together with endothelial protein C receptor, accelerates the catalytic efficiency of this activation. Activated protein C proteolytically inactivates factor Va and factor VIIIa, the two most important activated cofactors of the coagulation cas-

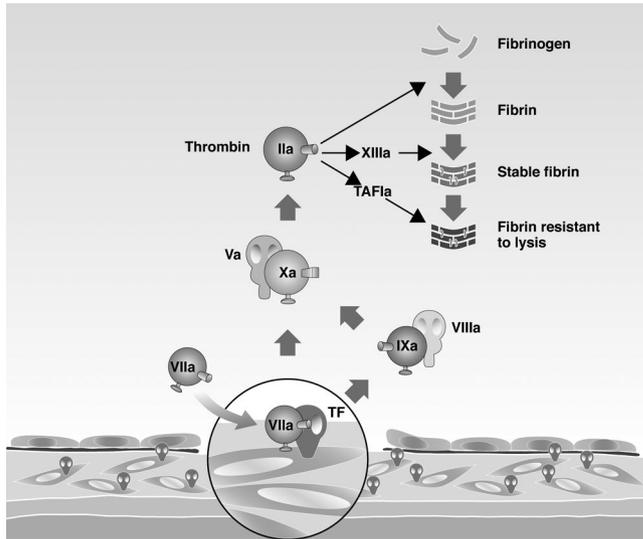


Figure 1. Role of tissue factor (*TF*) and coagulation factor VII in the activation of coagulation cascade leading to thrombin formation. *TAFIa*, thrombin-activatable fibrinolysis inhibitor; a, activated.

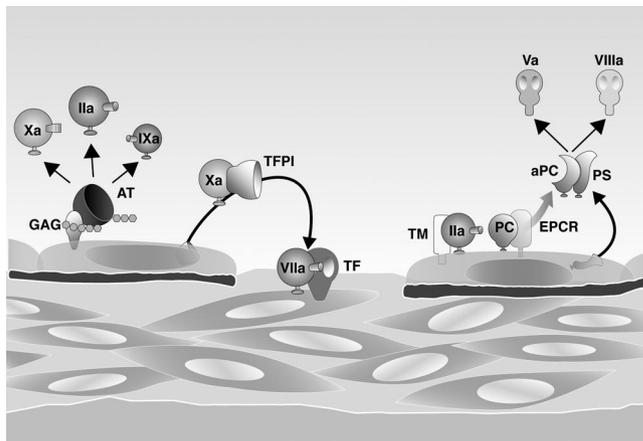


Figure 2. Anticoagulant mechanisms of blood coagulation. Antithrombin (*AT*) inhibits mainly activated factors II (*IIa*) and X (*Xa*) through its binding to glycosaminoglycans (*GAG*); protein C (*PC*), with its cofactor protein S (*PS*), is activated by thrombomodulin (*TM*) and inhibits activated factors V (*Va*) and VIII (*VIIIa*) through its binding to endothelial protein C receptor (*EPCR*). *TFPI*, tissue factor pathway inhibitor; a, activated.

Table 1. Inherited, acquired, and mixed coagulation or metabolic risk factors for venous thrombosis

Inherited	Acquired	Mixed
Antithrombin deficiency	Antiphospholipid syndrome	Hyperhomocystinemia
Protein C deficiency		Increased fibrinogen levels
Protein S deficiency		Increased factor VIII levels
Factor V Leiden		Increased factor IX levels
Prothrombin G20210A		Increased factor XI levels

cade, dramatically slowing the rate of thrombin and fibrin formation. The inhibitory effect of activated protein C is accelerated by its main cofactor, protein S (18). The inherited deficiency of one of these inhibitors leads to a critical reduction of the natural anticoagulant system and enhances thrombin generation, increasing susceptibility to venous thrombosis (17).

The two most common genetic risk factors for venous thrombosis are the G1691A mutation in the factor V gene (factor V Leiden) and the G20210A mutation in the prothrombin gene. The Leiden gain-of-function mutation consists of the substitution of an arginine by glutamine at position 506 of coagulation factor V (R506Q), which is the cleavage site for activated protein C in the factor V molecule (19). Mutant factor V is resistant to inactivation by activated protein C, leading to a hypercoagulable state and an increased susceptibility to venous thrombosis. Factor V Leiden explains >90% of cases of activated protein C resistance (20). The G20210A mutation in the prothrombin gene is a G-to-A transition at nucleotide position 20210 in the 3'-untranslated region of the coagulation factor II (prothrombin) gene (21). This gain-of-function mutation causes high levels of plasma prothrombin and heightened thrombin formation, with a resulting increased risk of venous thrombosis. Each of these mutations also increases the risk of atherothrombosis, but to a smaller degree (22).

Hyperhomocysteinemia is a mild risk factor for thrombosis attributable to an impairment of the metabolic pathway that transforms the amino acid methionine into cysteine, leading to an abnormal elevation of plasma concentrations of homocysteine, an intermediate product of this pathway. Genetic factors (e.g., gene mutations in methylenetetrahydrofolate reductase and cystathionine β -synthase) and acquired factors (e.g., deficiencies of folate, vitamin B₁₂, and vitamin B₆, advanced age, chronic renal failure, and the use of antifolate drugs) interact to determine plasma homocysteine concentrations, so that hyperhomocysteinemia is a mixed risk factor for both arterial and venous thrombosis (23). The possible mechanisms by which hyperhomocysteinemia contributes to thrombosis are multiple and still undergoing study; they include a toxic effect on endothelial cells, smooth muscle cell proliferation and intimal thickening, impaired generation of

nitric oxide and prostacyclin, increased platelet adhesion, activation of factor V, interference with protein C activation and thrombomodulin expression, induction of tissue factor activity, and inhibition of tissue plasminogen activator (24).

An association between increased plasma levels of some coagulation factors (VIII, IX, XI, and fibrinogen) and an increased risk of venous thrombosis has been demonstrated (25). The plasma levels of these factors are influenced by age and inflammation but are also under genetic control. The mechanisms by which increased factor levels in plasma enhance the risk of thrombosis are unknown, but a shift in the balance of the coagulation process toward a procoagulant state is plausible. There is much less (or no) association between high factor levels and atherothrombosis.

The antiphospholipid antibody syndrome is one of the most important acquired risk factors for thrombosis. Characterized by the presence of circulating antiphospholipid antibodies in plasma, it is associated with the presence of a history of arterial and venous thrombosis and/or pregnancy morbidity, including fetal loss. The clinically relevant antiphospholipid antibodies include lupus anticoagulant, anticardiolipin, and anti- β_2 -glycoprotein I antibodies. They are not directed against phospholipids *per se*, but against a wide variety of protein cofactors acting on phospholipid membrane surfaces (β_2 -glycoprotein I, prothrombin, protein C, protein S, annexin V, coagulation factor XII, and others). The resulting complexes interact with several cell types, including endothelial cells, monocytes, and platelets, all of which play an important role in hemostasis and thrombogenesis. The indirect activation of these cells results in the release of prothrombotic and proinflammatory mediators (e.g., tissue factor-bearing microparticles, interleukin (IL)-6, proteins of the complement system), leading to the activation of platelet and coagulation pathways (26).

Metabolic Syndrome

There is increasing evidence for an association between atherothrombosis and the metabolic syndrome, a cluster of risk factors for cardiovascular disease (27). They include glucose intolerance (ranging from type 2 diabetes mellitus to impaired glucose intolerance or impaired fasting glycemia), insulin resistance, ab-

dominal obesity, atherogenic dyslipidemia, and arterial hypertension. One of the most widely used definitions of the metabolic syndrome was proposed in 2001 by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and is based on the presence of at least three of the following diagnostic criteria: elevated waist circumference (abdominal obesity), elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting glucose (28–30). The metabolic syndrome is frequently accompanied by a prothrombotic state. This includes elevated plasma levels of PAI-1, thrombin-activatable fibrinolysis inhibitor, von Willebrand factor, coagulation factors VIII, VII, XIII, and fibrinogen, tissue factor, increased release of endothelial cell microparticles, and decreased protein C levels. Furthermore, patients with the metabolic syndrome exhibit endothelial dysfunction (mainly decreased production of nitric oxide and prostacyclin) and heightened platelet reactivity (27). The activation of the hemostatic system related to the metabolic syndrome has been mainly attributed to the action of proinflammatory and proatherogenic mediators (e.g., leptin, tumor necrosis factor [TNF]- α , IL-6) released by adipose cells (31), to a triggering effect of very-low-density lipoprotein and remnants of lipoproteins on platelet activation and PAI-1 gene expression (32), to the adverse effects of chronic hyperglycemia on fibrin structure and function (generating a clot more resistant to fibrinolysis) (33), and to an increase of circulating microparticles that support coagulation by exposure of anionic phospholipids and tissue factor (34).

Obesity may confer an increased risk for venous thrombosis independent of the metabolic syndrome. A high body weight can exert a mechanical impairment of the valve system in the deep veins of the lower limbs, with ensuing venous stasis, which is a risk factor for thrombus formation.

Previous Deep Vein Thrombosis

The presence of a residual thrombus after a first episode of deep vein thrombosis is an independent risk factor for recurrence (35). A potential mechanism by which the residual thrombus increases the risk of recurrence is impaired venous outflow, resulting in blood stasis and clot formation. However, because some pa-

tients have recurrent thrombosis in the initially unaffected leg and others have isolated pulmonary embolism, other mechanisms must be implicated. Residual thrombosis is perhaps a marker for a more generalized procoagulant diathesis. Elevated plasma D-dimer levels after withdrawal of oral anticoagulation (a marker of hypercoagulability) are an independent risk factor for recurrent venous thrombosis (36, 37).

Surgery, Immobilization, and Trauma

These transient conditions are associated with an increased risk of venous thrombosis because of a combination of stasis and local accumulation of tissue factor (i.e., hypercoagulability). Blood flow is relatively static in the pockets of venous valves, particularly those of the lower limbs. This effect is accentuated by immobilization. Stasis locally focuses various factors involved in the activation of hemostasis (cytokines and other mediators of inflammation), favors cellular margination and the interaction of circulating blood cells with endothelium, and is responsible for local hypoxia, one of the principal mechanisms of endothelial activation (38). However, studies in animals have shown that stasis alone does not provoke thrombosis (39). A local accumulation of tissue factor is needed.

Tissue factor is expressed by cells in the subendothelial compartment. Thus, physical disruption of the endothelium, as occurs in trauma or surgery, may lead to exposure of blood to extravascular tissue factor. However, the majority of venous thrombi occur in the context of an intact endothelium. In these cases, tissue factor may be expressed on the surface of activated endothelial cells and/or mononuclear cells that have been stimulated by any number of inflammatory mediators, including cytokines, chemokines (IL-1, IL-6, and IL-8, TNF- α , monocyte chemoattractant protein-1), vascular endothelial growth factor, factors derived by complement activation (C5a and complement membrane attack complex), immunocomplexes and antibodies, P-selectin, hemodynamic stress, hypoxia, and cell-cell interactions (38, 40). In addition to expressing tissue factor on their cell surface, activated cells (e.g., endothelial cells, monocytes, leukocytes, and platelets) may release tissue factor-rich and phospholipid-rich microparticles that circulate in the bloodstream (41). These mi-

croparticles can then interact with other cells through the action of adhesive proteins. For example, P-selectin glycoprotein ligand-1 facilitates the transfer of P-selectin from platelets or endothelial cells to microparticles of monocyte origin (42). These properties may facilitate thrombus propagation and activate coagulation in various sites. Finally, leukocytes and platelets can further enhance thrombosis through their expression of tissue factor under inflammatory stimuli (C5a, bacterial peptide, peptide N-formyl-methionine-leucine-phenylalanine, P-selectin) and platelet agonists (adenosine diphosphate, collagen, thrombin), respectively (43).

Cancer

The pathophysiology of venous thrombosis in patients with cancer is even more complex than in those without. Cancer may create stasis by compression and invasion of vessels. Tumor cells may promote the release of tissue factor from the affected organs during expansion and the metastatic processes. Importantly, cancer cells themselves may release tissue factor-rich microparticles. These microparticles can then adhere to (and be incorporated into) monocytes and other cells, particularly those activated by hypoxia, and promote fibrin formation (44, 45). Finally, tumor cell-derived inflammatory and proangiogenic cytokines (e.g., TNF- α , IL-1, and mostly vascular endothelial growth factor) may induce tissue factor expression in endothelial cells and monocyte-macrophages.

Oral Contraceptives and Hormone Therapy

Women using oral contraceptives are at increased risk for venous and arterial thrombosis. Mechanisms include a direct effect of estrogens on the vascular wall, changes in factors that promote endothelial dysfunction, and changes in coagulation factors. Studies in animals suggest a loss of the normal elastic configuration of the aorta, significant intimal thickening, and an increase in endothelial permeability after administration of oral contraceptives (46). There are also a few reports of increased venous distensibility and reduced blood flow in women using oral contraceptives (47). A possible explanation may be an estrogen-induced dose-dependent increase in the expression of matrix metalloproteinases that cleave

collagen and elastin in the vascular intima. The loss of venous tone, with the accompanying tendency to venous stasis, increases the risk of venous thrombosis. Oral contraceptives may increase the risk of arterial thrombosis by promoting endothelial dysfunction. However, this is a poorly investigated area, and it is not established how much these changes matter in the pathophysiology of thrombosis in oral contraceptive users (48).

Another mechanism increasing the thrombotic risk, particularly for atherothrombosis in women using oral contraceptives, is linked to changes in lipids and lipoprotein metabolism. Oral contraceptives result in an increase in total cholesterol primarily attributable to increases in low-density lipoprotein cholesterol. Furthermore, high-density lipoprotein cholesterol decreases and triglyceride levels increase, because of the effect of estrogen. Estrogens also affect lipoprotein metabolism by increasing the hepatic synthesis of apolipoproteins, or they may induce changes in hormones that affect lipoprotein metabolism, such as cortisol, thyroxine, or growth hormone (49, 50). Progestogen-only oral contraceptives have generally no or little effect on plasma lipoprotein levels.

Oral contraceptives modify the plasma levels of several coagulation factors (Table 2). However, these changes are often modest and concentrations of coagulation factors usually remain within the normal range. Oral contraceptive-mediated alterations in coagulation factor levels may result in synergistic or opposing effects on the risk of venous thrombosis. Levels of the anticoagulant proteins antithrombin and protein S decrease during oral contraceptive use, whereas protein C levels may increase (51, 52). The greatest effects have been seen with preparations containing the highest estrogen doses. An important effect of oral contraceptives on blood coagulation is the development of an acquired resistance to activated protein C caused, at least in part, by the increase in factor VIII. This phenomenon, as well as other changes in coagulation factors, appear to be more pronounced in women using third-generation preparations, i.e., those containing desogestrel, than in those using the second-generation preparations containing levonorgestrel (53, 54), although the difference is debated (55). Oral contraceptives also affect the fibrinolytic system, reducing PAI-1 levels and increasing levels of thrombin-activatable fibrinolysis inhibi-

Table 2. Hemostatic changes during oral contraceptive use and pregnancy

Factors	Change During OC Use	Change During Pregnancy
<i>Procoagulant factors</i>		
Fibrinogen, V, VII, VIII, IX, X, XII	↑	↑
XI	= or ↑	↓
von Willebrand factor	=	↑
<i>Anticoagulant proteins</i>		
Antithrombin	↓	=
Protein C	= or ↑	=
Protein S	↓	↓
Resistance to activated protein C	↓	↓
<i>Markers of thrombin formation</i>		
F1 + 2, TAT complexes, fibrinopeptide A, D-dimer	↑	↑
<i>Fibrinolytic factors</i>		
TAFI, PAI-1, PAI-2	↑	↑
t-PA	↓	↓

↑, increase; ↓, decrease; =, no change, compared to nonuse of oral contraceptives and to the nonpregnant state.

OC, oral contraceptive; F1 + 2, prothrombin fragment 1 + 2; TAT, thrombin-antithrombin complex; TAFI, thrombin-activatable fibrinolysis inhibitor; PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator.

tor and D-dimer. The overall increase in thrombin generation in women using oral contraceptives has been recently established by means of the endogenous thrombin potential test, i.e., the area under the thrombin generation curve, that is able to identify a global hypercoagulable state and is higher in oral contraceptive users than in nonusers (48, 51, 52).

Pregnancy

As discussed in this issue, normal pregnancy represents a hypercoagulable state. Pregnancy is associated with hemostatic changes that include increased concentrations of most procoagulant factors, decreased concentrations of some of the natural anticoagulants, and reduced fibrinolytic activity (Table 2). These changes help to maintain placental function during pregnancy and minimize blood loss at parturition. However, they may also predispose to maternal thrombosis and placental vascular complications. Plasma concentrations of coagulation factors V, VII, VIII, IX, X, XII, fibrinogen, and von Willebrand factor increase significantly during pregnancy, whereas factor XI levels tend to decrease. Total and free protein S decrease, whereas protein C and antithrombin remain substantially unchanged (56, 57). Activated protein C resistance, likely caused by increasing factors V and VIII and decreasing protein S (58), is frequently observed in pregnancy. The activation of coagulation shown by increasing

levels of prothrombin fragment 1 + 2, thrombin-antithrombin complex, fibrinopeptide A, and D-dimer (57, 58) occurs during the whole gestational period but is more pronounced in the third trimester. The fibrinolytic system is also impaired during pregnancy, as shown by increased plasma levels of thrombin-activatable fibrinolysis inhibitor, PAI-1 and PAI-2 (the latter of placental origin), and decreased tissue plasminogen activator activity (58, 59). Tissue factor is largely expressed in the placenta and is markedly increased in the amniotic fluid but not in plasma (59). Tissue factor and thrombomodulin are involved not only in hemostasis but also in the differentiation of placental blood vessels (60). Placental detachment at delivery with the ensuing release of placental substances at the site of separation is responsible, together with postpartum hemoconcentration, for the particularly high thrombotic risk of the postpartum period (61). Three weeks after delivery, blood coagulation and fibrinolysis have generally returned to normal (62).

Air Pollution

Over the past decade, a growing body of epidemiologic and clinical evidence has led to a heightened concern about the deleterious effects of air pollution on atherothrombotic cardiovascular disease (63–65). Among air pollutants, particulate matter <10 μm in aerodynamic diameter (PM₁₀) is of special interest. Potential mechanisms leading to cardiovas-

cular disease include autonomic dysfunction, systemic and local inflammation, endothelial injury, and alterations in the coagulation cascade (63, 64). Changes in heart rate and heart rate variability, arrhythmias, increase in markers of inflammation and tissue damage such as C-reactive protein, cytokines, interleukins, and serum lipids are conditions induced by air pollution that affect the cardiovascular system (64). Experimental and epidemiologic studies evaluating plasma concentrations of coagulation factors in association with air pollution exposure have produced different results. Whereas some studies have found increased levels of factor VII, fibrinogen, and von Willebrand factor, others showed decreased levels or no change (66). More recently, a novel association between air pollution and hypercoagulability has been observed both in healthy individuals and in patients with deep vein thrombosis (66–68). Air pollution is associated with a shortened prothrombin time in healthy subjects (66) and increased total plasma homocysteine levels in smokers (67). A large case-control study (68) showed that high mean PM₁₀ levels in the year before venous thrombosis were associated with a significantly shortened prothrombin time, and that each increase of 10 μg/m³ in PM₁₀ was associated with a 70% increase in thrombotic risk. Such effect was absent in women who used oral contraceptives. Because the aforementioned coagulation changes induced by air pollution are similar in characteristics and degree to those observed in oral contraceptive users, it may be that coagulation is already activated by oral contraceptives so that no further enhancing effect is observed after PM₁₀ exposure.

Travel

In the past decade, a growing body of evidence for an association between venous thrombosis and travel, particularly air travel, has become available. There are several plausible explanations for this association. In addition to immobilization, flight-specific factors, such as hypobaric hypoxia, may affect the coagulation system, enhance thrombin generation, and reduce fibrinolysis. Immobilization and sitting position are associated with an increased risk of venous thrombosis. Tall individuals are particularly vulnerable because of cramped seating, whereas short individuals whose feet do not touch the floor may experience extra compression

of the popliteal veins (69). Thrombin generation has been evaluated in several studies through measurements of prothrombin fragment 1 + 2 and its inhibitor complex thrombin-antithrombin complex. Activation of the fibrinolytic system is reflected by increased levels of D-dimers and decreased levels of tissue plasminogen activator and PAI-1. Previous studies investigating the effect of prolonged immobilization on thrombin generation and on the fibrinolytic system have yielded conflicting results (70). However, the majority of these reports lacked a control group. The only controlled study published to date (71) failed to find a difference in prothrombin fragment 1 + 2, thrombin-antithrombin complex, and D-dimers between travelers and nontravelers. The effect of hypoxia (attributable to decreased cabin pressure) on coagulation has been investigated both in hypobaric and normobaric conditions. The results during hypobaric, but not normobaric, hypoxia supports activation of the coagulation and fibrinolytic systems, reflected in a shortened activated partial thromboplastin time, decreased levels of fibrinogen and factor VIII (72), factor VII antigen and tissue factor pathway inhibitor (73), increased levels of D-dimers (72), prothrombin fragment 1 + 2, thrombin-antithrombin complex, and factor VIIa-tissue factor complex (73, 74). However, two other studies found no difference in markers of thrombin generation during hypobaric or normobaric hypoxia (75, 76). Fibrinolysis was more activated during air travel than during immobilization, as shown in a recent crossover study (77).

CONCLUSION

A large body of research over the past 20 yrs has improved our understanding of the biochemical processes involved in the pathogenesis of thrombus formation in arteries as well as in veins. We are beginning to understand that changes in blood coagulation, inflammation, and immune response are intricately linked and interdependent. Heightened generation of thrombin, the ultimate enzyme involved in coagulation and platelet activation and also an important cell-signaling effector molecule, is critical not only in the development of venous thrombosis but also in atherothrombosis. A common pathogenic determinant of venous and arterial thrombosis appears to be inflammation, although a clear cause-effect relation-

ship between such inflammation markers as interleukins, TNF- α , and monocyte chemoattractant protein-1 and thrombosis is not established yet.

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