REVIEW ARTICLE

Coagulation and the vessel wall in thrombosis and atherosclerosis

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KEYWORDS

atherosclerosis, coagulation, endothelium, thrombosis, vessel wall

ABSTRACT

The blood coagulation system is a key survival mechanism that has developed to protect man against lethal bleeding. A second function of blood coagulation is its close interaction with immunity. The immune-mediated coagulation responses may broadly be regarded as an element of response to injury. Pathological coagulation responses, including thromboembolism and disseminated intravascular coagulation (DIC), could therefore be regarded as excessive immune responses to a vessel wall injury. Virchow's triad, which comprises changes in the components of the blood, the state of the vessel wall, and the blood flow, was originally proposed for venous thrombosis. However, lately it appears that the same principles can be applied to arterial thrombosis and even DIC. It has even been postulated that all forms of thrombosis may be part of a continuous spectrum of the same disease. Over the past few years, an accumulation of evidence has shown that the etiopathogenetic mechanisms behind venous and arterial thrombosis are quite similar. The traditional elements of Virchow's triad are found to apply to both arterial and venous thrombosis. Yet, nowadays more emphasis is placed on the vessel wall and vascular bed specificity and the interaction with inflammation and hypercoagulability. This narrative review will discuss recent advances in research on the possible interactions between coagulation, the vascular endothelium, and atherosclerosis as well as the consequences of such interactions for venous and arterial thrombosis.

Introduction The blood coagulation system is a key survival mechanism that has developed to protect man against lethal bleeding. A second function of blood coagulation, which has only recently received more attention and recognition, is its close interaction with immunity. The immune-mediated coagulation responses may broadly be regarded as an element of response to injury. Along this line, pathological coagulation responses, including thromboembolism and disseminated intravascular coagulation (DIC), can be regarded as excessive immune responses to a vessel wall injury. Classically, three distinct forms of thrombosis are known: venous, arterial, and the mixed, microvascular form (DIC). Thrombosis can be local in origin, such as in deep vein thrombosis of the leg or in cerebral venous sinus thrombosis, but can likewise manifest itself systemically, such as with DIC affecting primarily the microvasculature. On top of this, a focal occurrence may also cause a more distant pathology as manifested by pulmonary embolisms.

The triad predisposing to thrombus formation postulated by Virchow comprises changes in the components of the blood, the state of the vessel wall, and the blood flow. It was originally proposed for venous thrombosis. However, lately it appears that the same principles can be applied to arterial thrombosis and even DIC. It has even been postulated that all forms of thrombosis may be part of a continuous spectrum of the same disease.[1] A more contemporary triad includes the identical components, but they are much better characterized than in Virchow's days. Abnormal blood constituents are represented by abnormalities in platelet function, coagulation, or fibrinolysis factors and are influenced by metabolic, hormonal, and inflammatory elements. Vessel wall changes are nowadays also better characterized with most arterial

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Received: November 5, 2012
Accepted: November 8, 2012
Published online: November 15, 2012
Conflict of interest: none declared.
Pol Arch Med Wewn. 2012; 122 (11): 557-566

thrombosis developing on underlying atherosclerotic pathology. In the atherosclerotic artery, changes in hemorheology and/or turbulence at bifurcations and stenotic regions enable the formation of local arterial thrombosis.[2-4] In contrast, in venous thrombosis, one of the primary events is impaired oxygenation of the venous endothelium evoked by impaired venous flow, triggering inflammation.

In all forms of thrombosis, coagulation and inflammation are two principal pathways that act hand in hand in a "response-to-injury" scenario. Despite many differences in the contributing factors, the main interface appears to be the vascular endothelium, serving as the critical regulator of flow, hypercoagulability, and thrombosis. The endothelial involvement depends in its responses on the dynamic interplay between the vessel wall and the blood compartment. The coagulation system plays an important role in maintaining endothelial integrity as well as in initiating or accelerating pathophysiology leading to thrombosis. In addition, the endothelium is not a single entity but is highly heterogeneous in its phenotype and behavior, which may be relevant to the localization of thrombosis. In atherosclerosis, coagulation proteases play a major role, at least in experimental conditions, while the clinical relevance remains to be demonstrated.

Several pathophysiological conditions can alter one or more of the components of Virchow's triad leading to an activation of coagulation with in general, involvement of all three components being required to generate thrombosis. In venous and arterial thrombosis, several risk factors are shared, including obesity, diabetes mellitus, age, and hypertension, also suggesting a link between venous and arterial thrombosis.[5-8] Indeed, recent studies show that patients with idiopathic venous thrombotic disorders are at a higher risk of developing arterial thrombotic complications than matched controls.[9] Both with regard to atherosclerosis and thrombosis, the type and duration of anticoagulation may have clinical consequences that need to be addressed.

This narrative review will discuss recent advances in research on the possible interactions between coagulation, the vascular endothelium, and atherosclerosis as well as the consequences of such interactions for venous and arterial thrombosis.

Mechanisms leading to thrombin generation Hemostasis is a highly conserved mechanism throughout species, aimed at protecting against lethal bleeding. In all mammals, blood coagulation involves both a cellular and a protein component. The coagulation process is a dynamic, highly interwoven array of multiple processes. In the context of this review, we will only address elements of the coagulation cascade that lead to generation of thrombin, along the lines discussed in our review paper on coagulation and atherosclerosis.[9] Therefore, we will not focus on the important role of platelets in complex processes such as atherosclerosis; for this, we refer the reader to other reviews on these topics.

Coagulation starts with the exposure of tissue factor (TF), followed by a stepwise activation of coagulation zymogens, and culminating in the generation of thrombin. Thrombin, a key regulator of coagulation, then converts fibrinogen into fibrin.[10] Cellular TF binds small amounts of factor (FVII) present in the circulation, but also activates the conversion of FVII into FVIIa. The TF–FVIIa complex in turn activates FIX and FX leading to the formation of a small amount of thrombin. The thrombin feedback loop results in the activation of FXI into XIa that additionally activates FIX leading to further amplification of the intrinsic cascade. In this process, thrombin activates the cofactors V, VIII, and the FXIII zymogen, which leads to enhanced thrombin and fibrin formation (FXIIIa cross-linking fibrin monomers to form a polymerized clot). The end result of all these sequential reactions is the acceleration of fibrin formation at a specific time and place when this is required (e.g., bleeding).[10]

Excess fibrin formation is limited by several anticoagulant mechanisms. These include TF pathway inhibitor (TFPI), which limits TF–FVIIa--mediated FXa formation, in a protein S-dependent manner (at low TF concentrations).[11] In addition, thrombin serves an anticoagulant role in binding the cell surface receptor, thrombomodulin (TM), whose complex converts protein C into activated protein C (APC). APC proteolytically inactivates the activated FV and FVIII, reducing the rate of thrombin generation. Additionally, free thrombin can be quenched by the serine protease inhibitor antithrombin (AT) into a thrombin–antithrombin complex (TAT).

Under physiological conditions, a basal level of activated coagulation is maintained in a TF--dependent manner.[12] This low-level activity provides a flexible system that can rapidly respond to injury. Vascular endothelial disruption triggers the coagulation cascade, but also the fibrinolytic pathway. This pathway is initiated by endothelial cell-derived tissue plasminogen activator (tPA), which mediates the conversion of plasminogen into plasmin. Plasmin will then degrade fibrinogen and fibrin, thereby limiting the size of the formed clot and furthermore clearing the clot once the endothelial damage has been repaired. Other proteins, such as α_2-antiplasmin and plasminogen activator inhibitor-1 (PAI-1), inhibit the fibrinolytic pathway. Fibrinolysis is also controlled by thrombin-activatable fibrinolysis inhibitor (TAFI), which removes C-terminal residues from fibrin that are important for the binding and activation of plasminogen. This way, both coagulation and fibrinolysis are regulated in a fine-tuned, complex manner (FIGURE 1).

Vessel wall The vascular endothelium can be regarded as a mediator between the components of Virchow's triad, for both anatomical

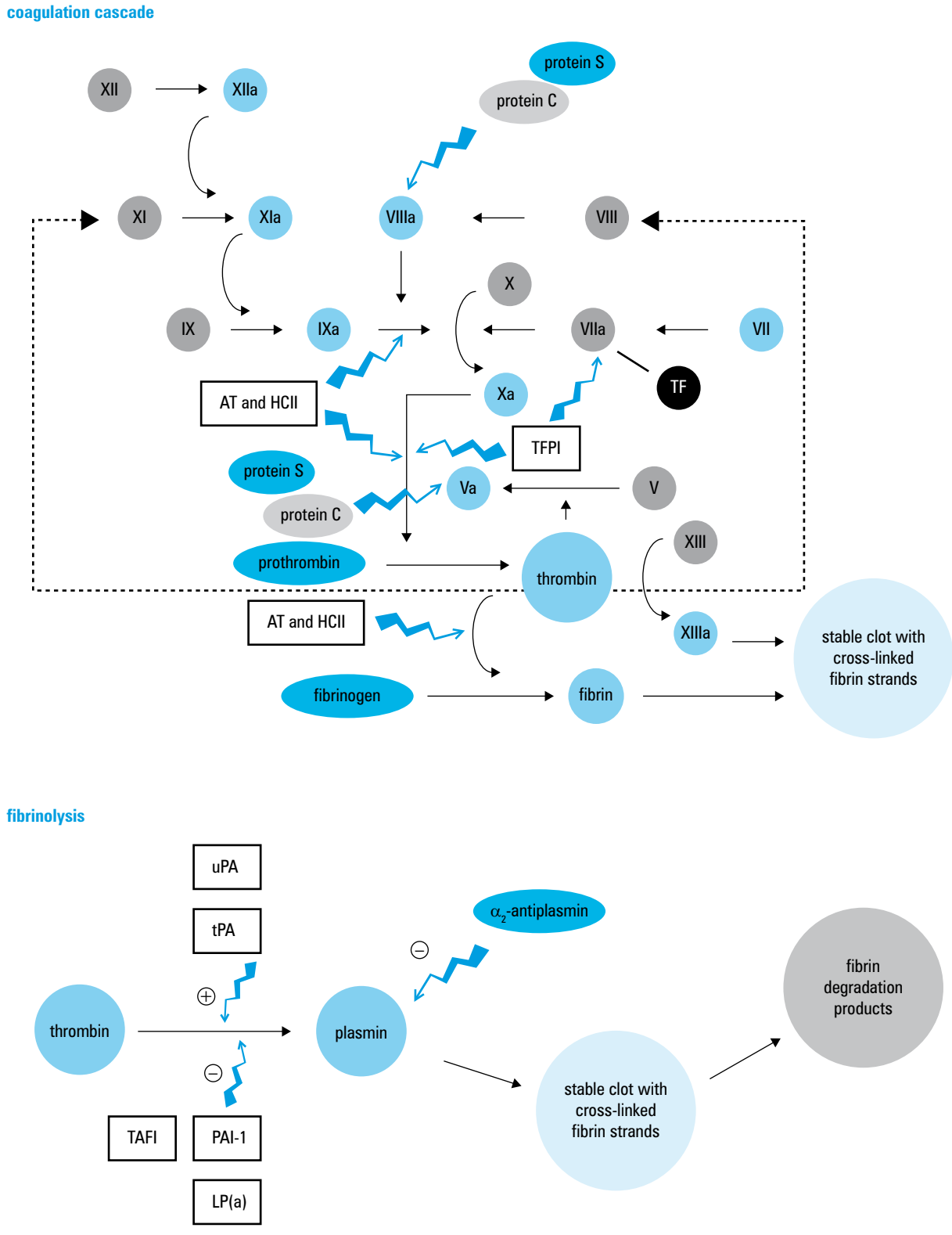

FIGURE 1 Coagulation cascade and fibrinolytic process

Abbreviations: AT – antitrombin, HCII – heparin cofactor II, LP(a) – lipoprotein(a), PAI-1 – plasminogen activator inhibitor-1, TAFI – thrombin-activatable fibrinolysis inhibitor, TF – tissue factor, TFPI – TF pathway inhibitor, tPA – tissue plasminogen activator, uPA – urokinase plasminogen activator

and functional reasons.[13] Recently, endothelial dysfunction has emerged as the most important constituent of Virchow's contemporary triad due to its ability to strongly influence the other constituents of hemostasis. Furthermore, it also affects its natural sequels, inflammation, and tissue repair.[2,13]

Endothelial cells are located at the demarcation between tissue and blood and therefore are crucial for the protection against vascular injury and the maintenance of blood fluidity.[14] Endothelium across the vascular bed does not consist of a collective of identical cells, but should be regarded as a heterogeneous conglomerate of cells with diverse structure and function.[15] Adding to this,

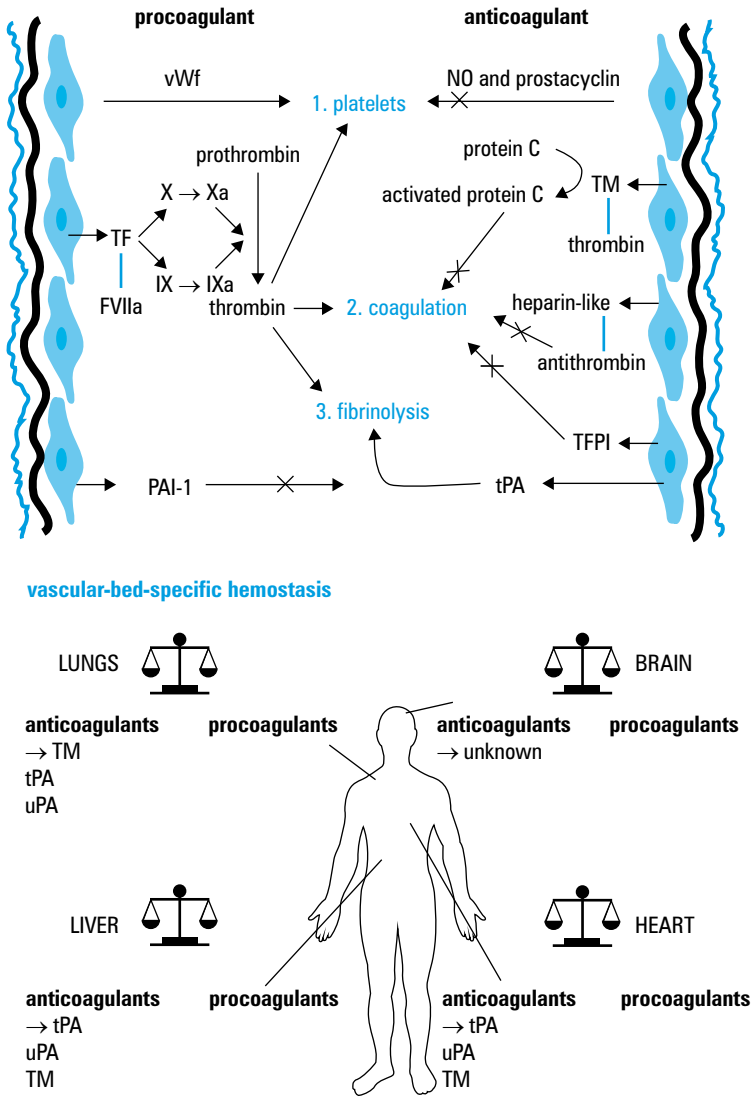

FIGURE 2 **A** – hemostasis is mediated by the balance of procoagulants vs. anticoagulants; procoagulant activities of the endothelium are the expression of receptors for cell-surface tissue factor (TF) and the release of von Willebrand factor (vWf), plasminogen-activator inhibitor type 1 (PAI-1); anticoagulant forces of the endothelium are, besides providing the nonthrombogenic cell-surface membrane, the release of heparin sulfate and prostacyclin, the expression of thrombomodulin (TM), tissue-type plasminogen activator (tPA) and endothelial nitric oxide (NO) synthase (modified from Wu et al.[14])

B – the components for the balance between procoagulant forces and anticoagulant forces vary per vascular bed

Abbreviations: see FIGURE 1

endothelium possesses a structure and function that can alter in space and time, under the influence of sickness and health. It is, therefore, important to distinguish normal from disturbed endothelium.[16,17] The endothelium, under normal circumstances, supports vasodilatation, inhibits adhesion and activation of blood platelets, quenches the coagulation cascade while amplifying fibrinolysis and antagonizing inflammatory processes and is consequently considered to be antithrombotic and anti-inflammatory.

The endothelium can be regarded to be as important for hemostasis as the liver. However, while the liver constantly synthesizes coagulation zymogens, the pro- and anticoagulants produced by the endothelium are both regulated and site-specific.[15]

Four mechanisms have been described that contribute to the inhibition of fibrin deposition on a normal endothelium[13]: 1) the glycocalyx produces heparan- and dermatan-sulfate molecules that activate heparin cofactor II and antithrombin; 2) the expression of TFPI limits the activity of the extrinsic pathway; 3) the activation of the protein C /protein S system downregulates the intrinsic coagulation route; the endothelial protein C receptor (EPCR) mediates APC's effects on endothelium and other vessel wall cells; 4) the expression of tPA and urokinase stimulates fibrinolysis.

These four mechanisms are not regulated evenly distributed over the vascular tree, but are probably site-specific. Based on the limited evidence available, it seems that large vessels mainly express EPCR, microvessels express TFPI, and the pulmonary and cerebral arteries primarily tPA. TM is present in all endothelial cells, being prominent in the microvessels of the lung, yet only minimally present in the blood-brain barrier (FIGURE 2).[14,18] In response to systemic inflammation, an alteration of this site-specificity has been observed.[15] This alteration can be caused by signals from the microenvironment around the endothelial cells (e.g., through cytokines, mechanical forces, components of the extracellular matrix, and surrounding cells), which are converted through endothelial cell-signaling networks and can lead to alterations in the mRNA expression of hemostatic proteins and their function.[19-21] If problems occur in the synthesis of coagulation factors by the liver (for example due to impaired liver function in cirrhosis), a hemostatic imbalance can arise within the vascular system. This systemic imbalance can, however, be counteracted to some extend via site-specific responses of the endothelium.[15,21] Clinically, it is therefore possible that with the loss of function of one of the liver generated natural anticoagulants, such as protein C, while one would expect a diffuse hypercoagulability, only local thrombotic lesions in discrete vascular segments are seen.[21] This supports a model of the so called "vascular-bed-specific hemostasis," and it seems credible that this model may be applicable to both venous and arterial vasculature.

Interplay between coagulation and the endothelium of the vessel wall When perturbation of the endothelium occurs, either in the course of hemostasis (arresting bleeding) or in prothrombotic conditions, the overall response of the endothelium will be a local prothrombotic, procoagulant, and proinflammatory state. Concurrent functional endothelial alterations include the enhancement of permeability, the production of cytokines and growth factors as well as the increase in the expression of chemokines, leukocyte, and platelet adhesion molecules (e.g., vascular cell adhesion molecule [VCAM], intercellular adhesion molecule [ICAM]).[13]

Inflammation triggers a downregulation of TM synthesis leading to a decrease in protein C activation and an increase in PAI-1 production. Synergistically, the endothelial cells start to express TF and procoagulant FV in response to inflammatory mediators (e.g., tumor necrosis factor-α [TNF-α] and interleukin [IL]-1).[22,23] These collective alterations then in turn enhance local fibrin deposition to the vessel wall. The changes in permeability of the vessel wall further promote the passage of inflammatory cells and coagulation proteins into the vessel wall stimulating local production of thrombin, a prothrombotic, but also proinflammatory enzyme. It is, therefore, clear that endothelial dysfunction is an important constituent of Virchow's triad leading to a site-specific upregulation of coagulation and thereby increasing the risk of thrombosis.

In addition to these inflammation-dependent mechanisms, serine proteases, such as FVIIa and FXa, and thrombin can directly act on vessel wall cells, through the activation of the so called protease-activated receptors (PARs).[24] As with many coagulation proteases, the net effects of thrombin activation of PAR-1 may act in two apparently opposite ways. For instance, thrombin activation can on the one hand lead to endothelium-dependent vasodilatation (through PAR-1), but on the other hand also induce vasoconstriction.[25-31] Furthermore, various studies have proposed a role for thrombin in causing an increase in the permeability of the endothelium, thus disrupting the endothelial barrier function.[32-34] Theoretically, it is difficult to classify the resulting phenotypical endothelial changes as either "positive" or "negative", as a balance between those is probably essential for adequate immune responses, wound healing, and tissue repair. We have to consider the interaction between coagulation and vascular endothelium in a time-, location-, and situation-dependent manner. In addition, age may be a crucial factor. While in young individuals, endothelial cells will mostly be unperturbed, the cumulative exposure to cardiovascular risk factors, driving inflammatory mediators, provides an increasing challenge to the protective properties of endothelial cells at a more advanced age. This may be associated by a progressive decay in protective molecules such as TM and EPCR that have been shown to vanish from the endothelium upon increasing atherosclerosis.[35] Thus, the effects of essentially protective proteases, such as thrombin, may become more prothrombotic and proinflammatory in time, due to reduced reserve in anticoagulant and anti-inflammatory mechanisms. Therefore, one of the consequences of aging may be a shift from "positive" to "negative" functions of activated coagulation, in those at risk for cardiovascular disease, while protective functions may be maintained for a long time in those that maintain a healthy vascular system.[36]

The role of coagulation in atherosclerosis One of the recently discovered effects of thrombin that is considered "negative" is related to the pathophysiological process causing atherosclerosis. There is abundant (experimental) data showing that thrombin is a crucial mediator in the crosstalk between coagulation, inflammation, and the vessel wall. Although the impact that thrombin has on atherosclerotic development is a relatively novel topic of investigation, it has been observed that both in the early stages of atherosclerotic plaque formation and in the advanced stages of atherosclerosis with plaque progression and destabilization, thrombin is involved.

By generating proinflammatory mediators, thrombin stimulates the recruitment of monocytes and T cells into the vessel wall, encouraging early plaque formation. The signaling mechanisms that have a proatherogenic impact on the vessel wall are mainly mediated through PARs. When activated, the endothelium in turn expresses certain surface markers such as VCAM and ICAM allowing leukocyte adhesion and rolling. These actions are essential for further development and progression of atherosclerosis.[37]

Thrombin is also a potent mediator for the expression of selectins on the endothelium; it causes the expression of E-selectin on the endothelial surface and has the potential to release P-selectin from endothelial Weibel-Palade bodies.[38-40] Beside its effects on the endothelium, thrombin also induces effects on other parts of the hemostatic process stimulating atherogenesis. By targeting PAR-1 and PAR-4 receptors on the surface of human platelets, thrombin induces atherogenic signals, boosting the synthesis and release of proinflammatory mediators. Furthermore, it enhances the interaction between platelets and leukocytes to increase chemotaxis, adhesion, and the migration of leukocyte subsets (neutrophils) into the vessel wall. Thrombin activation of platelets leads to the expression of CD40 ligand on the platelet surface, resulting in downstream atherogenic signals to other cells including, once more, endothelial cells and smooth muscle cells. Several additional pathways implicating thrombin in the development of atherosclerosis including vascular smooth muscle proliferation and proangiogenic responses.[24]

Numerous experimental studies have indicated that hypercoagulability aggravates atherosclerosis in ApoE$^{-/-}$ mice, while mice with a defect in coagulation (e.g., hemophilia A) tend to be protected or may show phenotypic effects on atherosclerosis (fibrinogen deficiency).[10] However, the protective effect of hemophilia A is dependent on the genetic mouse background; while ApoE$^{-/-}$ mice were protected, the effect was absent in LDLR$^{-/-}$ mice. Since in humans, the protective effect of hemophilia on atherosclerosis is also disputed, it remains uncertain whether any atherosclerosis-modifying effect of coagulation proteases is confined to a genetically susceptible background (both in humans and

other mammals).[41] In addition, it is generally inferred from experimental studies that the effector mechanisms in atherosclerosis are mediated through thrombin generation and PAR activation, but protease-specific effects of fibrinogen, FXa, FVIIa-TF, and TFPI may also be relevant. As a proof of principle of the important role of thrombin, several studies showed that direct inhibition of thrombin (either by melagatran or dabigatran) protects against atherosclerosis development in ApoE$^{-/-}$ mice, suggesting that at least thrombin is a key enzyme in this context.[42,43]

Despite the experimental evidence suggesting that there is an association between inherited hypercoagulability and the development of atherosclerosis, clinical studies have so far shown conflicting results.[41,44-46] Early studies indicated that certain hypercoagulable states (e.g., prothrombin mutation 20210A and FV Leiden) were associated with arterial occlusive disease,[47,48] but later studies casted doubt on these observations by showing no such associations.[49] Based on these conflicting results, a large meta-analysis was performed in 2006 by Ye et al.[50] to investigate the association between certain hemostatic gene polymorphisms and coronary artery disease (CAD). It was found that FV Leiden and the prothrombin G20210A were moderately associated with the risk of CAD with the perallele relative risks for FV Leiden and of prothrombin G20210A being 1.17 (95% confidence interval [CI], 1.08–1.28) and 1.31 (95% CI, 1.12–1.52), respectively. Although these relative risks are small and make one wonder as to what the direct clinical implications should be, the results are biologically relevant and highlight the importance to gather more knowledge about the mechanisms behind hypercoagulability and (arterial) thrombotic events. When, for example, the two genetic defects are combined, the hazard ratio for ischemic heart disease increases from 1.5 (95% CI, 1.1–2.1) for the prothrombin G20210A mutation alone to 6.0 (95% CI, 2.0–19) in combination with the FV Leiden mutation, possibly explained by a common prothrombotic pathway.[51]

Effects of hypercoagulability on endothelium, thrombosis risk, and thrombosis location Now that it has been established that thrombin itself can cause endothelial disruptions and even promote atherosclerosis, one of the remaining questions is whether the thrombosis risk associated with "hypercoagulability" acts through upregulation of inflammation and perturbation of vascular endothelium. For this review, we consider "hypercoagulability" as a condition of the blood arising from an imbalance between pro- and anticoagulant forces and which can be driven by inherited and/or acquired factors. Over the past years, extensive research has further developed our understanding of the interplay between hypercoagulability and inflammation, also propagating venous thrombosis.[52]

Hypercoagulability can be congenital or acquired in origin. Although the effect of congenital deficiencies in any of the known anticoagulant proteins including antithrombin, protein C, protein S, as well as the FV Leiden and the prothrombin 20210A mutations on the risk of venous thrombosis has been firmly established, their actual contribution to inflammation and response to injury effects are poorly known in the clinical setting.[52,53] Interestingly, in experimental models of sepsis, defects in any of the TM–protein C, antithrombin, or TFPI pathways appear to have major influence on the defense against sepsis and the development of DIC. Animals with an inborn or acquired defect in any of these natural anticoagulant proteins were more vulnerable to die of sepsis and had more aggravated DIC. Several studies by the Taylor group established that intact levels and function of each of the natural anticoagulants AT, PC, or TFPI were relevant in baboons in order to survive severe sepsis.[54-56] These studies also provided the basis for the subsequent clinical intervention studies like PROWESS that appeared to herald a way of reducing mortality due to severe sepsis by infusing recombinant APC.[57] Unfortunately, subsequent studies failed to corroborate this protective effect and the drug has now been withdrawn.[58]

The overall lesson from the experimental studies may be that lack of or defect in any of the natural anticoagulant proteins may impair the immune defense in conditions of sepsis, resulting in an aggravated DIC response, mostly confined to the microvascular endothelium.

Whether the susceptibility to venous thrombosis in anticoagulant defective humans is also based on an increased inflammatory tendency remains to be proven.

Several acquired hypercoagulable conditions have been associated with an increased risk for both venour thromboembolism (VTE) and arterial thrombosis. These acquired hypercoagulable conditions include a variety of syndromes such as cancer, myeloproliferative syndromes, antiphospholipid syndrome, hyperhomocysteinemia, and heparin-induced thrombocytopenia.

Although thrombi related to these acquired hypercoagulable states may present as VTE, or even as arterial thrombosis, thrombosis can be seen in atypical vascular locations as well. Patients with the antiphospholipid syndrome have widespread thrombus formation in segments of both the venous and arterial vascular tree, including for example thrombosis in the retinal artery or vein.[59] Vascular bed specificity is applicable to the acquired hypercoagulable states caused by paroxysmal nocturnal hemoglobinuria (PNH) and myeloproliferative disorders. PNH has a predilection for intra-abdominal and cerebral vessels. Myeloproliferative diseases are characterized by a high incidence of thrombosis in the hepatic, portal, and mesenteric veins.[60] Recent research indicates for example that in a subpopulation of patients with the myeloproliferative disorder polycythemia vera,

which is associated with an increased rate of intra-abdominal thrombi, hepatic venule endothelial cells are affected by the malignant process.[61] Falanga et al.[62] have shown that such endothelial cells become procoagulant (by upregulation of TF and downregulation of TM) and that this phenotype can be corrected by the application of all-trans retinoic acid. The mechanism of hyperhomocysteinemia-related thrombosis is not yet established; however, it is known that human umbilical vein endothelial cells treated with homocysteine increase their externalization of procoagulant phosphatidylserine and shedding of procoagulant endothelial microparticles. Consequently, these changes lead to an enhanced clot-promoting activity of the endothelial cells.[63] With regards to the antiphospholipid syndrome, it has now been generally accepted that the endothelium is a predominant target of antiphospholipid antibodies. Pathogenic antibodies bind to the β_2-glycoprotein I causing a prothrombotic endothelial cell phenotype with an upregulated expression of TF and E-selectin, but an increased release of microparticles as well.[64] These diverse observations provide strong support for the existence of distinct interactions between the blood components and the local vessel wall, possibly depending on the type of endothelial cell present in both the venous and arterial vascular bed.

Association between venous thrombosis and atherosclerosis An association between VTE and atherosclerosis has been postulated. In separate studies, patients with an unprovoked VTE were shown to have a higher prevalence of carotid artery plaques, coronary artery calcium, and arterial thrombosis compared with healthy controls.[65-67] A recent review by Ageno et al.[68] showed that important risk factors associated with VTE were concordantly associated with atherosclerosis (e.g., obesity, hypertension, diabetes mellitus, and hypertriglyceridemia).[68] The nature of this association has not been clarified, but the risk factors all share effects on vascular endothelium. Inflammation-coagulation crosstalk may be at the basis of this observed risk interaction. As recently reviewed by Reitsma et al.,[52] venous thrombosis is characterized by several proinflammatory reactions involving expression of leukocyte adhesion molecules by the endothelium, activation of platelets secreting chemokines, and activation of neutrophils releasing neutrophil extracellular traps that act in different prothrombotic ways.[52] Since inflammation is at the basis of atherosclerosis as well, it may be inferred that ongoing inflammation may aggravate atherosclerosis, particularly in patients with a protracted course of idiopathic thrombosis. Since an increased risk of acute myocardial infarction was observed after VTE, it is also likely that plaque-destabilizing effects are involved.

Suggested implications for research and medical practice that have been stated are a modification of (atherosclerotic) lifestyle counseling in VTE patients and a potential role for prophylaxis with antiplatelet therapy and statins. Also, it becomes of interest to determine the effects of anticoagulant treatment beyond preventing (recurrent) thrombosis, on the inflammatory effects on the vessel wall.

Effects of anticoagulation on the vessel wall If we assume that hypercoagulability interacts with and affects the vessel wall through mediation via the endothelium, it is tempting to speculate on the possible effects of anticoagulation. Several researchers have postulated that the use of anticoagulant medication, through the inhibition of thrombin, could have beneficial effects on slowing down atherosclerosis. Anticoagulant medication is used for a variety of arterial and venous thromboembolic disorders, for the prevention as well as treatment of thrombosis. The commonly used vitamin K-antagonists (VKA) act directly on the inhibition of carboxylation by the liver of the so called vitamin K-dependent proteins (VKDP). When there is a deficiency of vitamin K or vitamin K is "blocked" with the use of VKA, the VKDPs will be nonfunctional and are called "proteins induced by vitamin K deficiency or antagonists". However, the desired effects VKA have on inhibiting coagulation may be overshadowed by the effect of VKA on the extra-hepatic VKDPs.[69] One of these VKDPs is the matrix gla protein (MGP) that is involved in the inhibition of calcification of the arterial vessel wall. MGP is synthesized locally in the vessel wall by smooth muscle cells and, likewise to the coagulation VKDPs, it needs vitamin K-dependent carboxylation for its function. It has been shown that MGP knock-out mice ($MGP^{-/-}$) die within a few weeks after birth due to complete calcification of the medium and large arterial vessels.[69-71] Limited experimental data suggest a protective effect of VKA treatment in $ApoE^{-/-}$ mice by large calcifications that stabilize the atherosclerotic plaque.[69] On the other hand, it has been stated that with large agglomerations of calcification present, microcalcifications are present as well, making the plaque vulnerable and prone to rupture. The research regarding the effect of VKA on vascular calcification in humans is relatively new; only since the beginning of this century studies concerning this topic have been published.[72-75] These studies strongly suggested that the use of VKA accelerates the process of calcification of the cardiac valves, the vessel wall, and in the atherosclerosis plaque; therefore, the use of VKA in certain patient populations could potentially be harmful.[69]

In the past few years, novel anticoagulants (NOACs), such as the direct thrombin- and factor Xa-inhibitors, have been introduced clinically. Quite clearly, it should be investigated what the effects of these NOACs are on the venous and arterial vascular bed. Unlike the VKAs, these NOACs do not seem to interfere with VKDPs and therefore not with MGP. However, they probably

do have pleotropic effects that could also interfere with atherosclerosis or vascular calcification. So far, only a handful of studies concerning this topic have been published. The direct thrombin inhibitor, melagatran, showed beneficial effects on both the size and composition of advanced atherosclerotic lesions in mice, possibly due to a reduced activation of proinflammatory transcription factors (NFκB and AP-1) and a decreased synthesis of MMP-9.[43] Dabigatran, another direct thrombin inhibitor, showed in ApoE$^{-/-}$ a reduced atherosclerotic lesion size and an improved endothelial function due to a decrease in oxidative stress and reactive oxygen species production in (hypercholesterolemic) atherosclerosis.[42,76] Administration of rivaroxaban, a direct FXa-inhibitor, in ApoE-deficient mice showed no effect on lesion progression; however, it did result in the downregulation of inflammatory mediator expression (of, for example, IL-6, TNF-α, monocyte chemoattractant protein-1, and Egr-1) and promoted stability of advanced atherosclerotic lesions.[77] These data appear to confirm the idea that thrombin (generation) is a relevant element in the process of atherosclerosis, at least in experimental animal models.

Conclusion Traditionally, the origin of thrombosis has been viewed separately for arterial and venous thrombosis, and the pathophysiology has been explained by distinct mechanisms and influenced by different risk factors. Over the past few years, however, there has been a paradigm shift due to the accumulation of evidence showing that the etiopathogenetic mechanisms behind venous and arterial thrombosis are quite similar. The traditional elements of Virchow's triad have been found to apply both to arterial and venous thrombosis. More emphasis is placed on the vessel wall and vascular bed specificity and the interaction with inflammation and hypercoagulability. The increased understanding of the interactions between endothelial dysfunction, vascular inflammation, thrombosis, and atherosclerosis opens possibilities for novel diagnostic and therapeutic approaches for both venous and arterial cardiovascular disease, including atherosclerosis.

Acknowledgements This research was performed within the framework of the Center for Translational Molecular Medicine (http://www.ctmm.nl), project INCOAG (grant no., 01C-201), and supported by the Dutch Heart Foundation. H.T.C. is a Fellow of the Gutenberg Research Foundation, Gutenberg University, Mainz, Germany.

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ARTYKUŁ POGLĄDOWY

Krzepnięcie krwi i ściana naczyniowa w zakrzepicy i miażdżycy

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krzepnięcie krwi, miażdżyca, ściana naczyniowa, środbłonek naczyń, zakrzepica

STRESZCZENIE

Krzepnięcie krwi stanowi kluczowy mechanizm zabezpieczający organizm człowieka przed śmiertelnym krwawieniem. Bliskie powiązanie z układem immunologicznym determinuje jego drugą funkcję – współdziałanie w odpowiedzi na uraz tkankowy. Patologie krzepnięcia krwi, takie jak choroba zakrzepowo-zatorowa czy zespół rozsianego wykrzepiania wewnątrznaczyniowego (*disseminated intravascular coagulation* – DIC), mogą być zatem uważane za skutek nadmiernej odpowiedzi immunologicznej na uszkodzenie ściany naczyniowej. Triada Virchowa, obejmująca zaburzenia w składzie i przepływie krwi oraz uszkodzenie ściany naczyniowej, została opisana dla zakrzepicy żylnej. Pojawia się jednak coraz więcej dowodów przemawiających za tym, że mogą one odgrywać rolę również w zakrzepicy tętniczej czy nawet DIC. Wysunięto nawet hipotezę, że poszczególne postacie zakrzepicy stanowią w istocie zespół zaburzeń tworzących spektrum tej samej choroby. Ostatnie lata badań przyniosły rozliczne dowody wskazujące na istnienie etiopatologicznych podobieństw pomiędzy zakrzepicą żylną i tętniczą. Tradycyjne elementy triady Virchowa dotyczą zarówno zakrzepicy żylnej, jak i tętniczej. Coraz więcej uwagi poświęca się dziś interakcji między ścianą naczynia i łożyskiem naczyniowym a procesami zapalnymi i nadkrzepliwością. W obecnym artykule przeglądowym omówimy najnowsze doniesienia naukowe dotyczące powiązań między układem krzepnięcia, śródbłonkiem naczyń i miażdżycą oraz ich konsekwencje dla rozwoju zakrzepicy żylnej i tętniczej.

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Praca wpłynęła: 05.11.2012.
Przyjęta do druku: 08.11.2012.
Publikacja *online*: 15.11.2012.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2012; 122 (11): 557-566
Tłumaczyła dr med. Anna Kalińska