Regulation of Vascular Bed–Specific Prothrombotic Potential

Jay M. Edelberg, Patricia D. Christie, Robert D. Rosenberg

Abstract—Hemostasis is the result of interdependent and complex systemic and local endothelial pathways that govern vascular integrity and rheology. A striking feature of hypercoagulable conditions is the focal nature of the resultant thrombotic pathology. Such disorders in hemostasis may be associated with distinct vascular beds, thus implying that the relative combined contribution of individual regulatory pathways may be specific and/or unique to a particular locale in the vasculature. Systemic factors and platelets mediate the formation of fibrin deposition; however, it is the diverse interrelationships in the interaction of these systemic elements with the local endothelial components that dictate vascular bed–specific hemostatic regulation. Indeed, the local activation of coagulation cascades, rather than increases in systemic thrombotic potential, is what leads to fibrin formation in different vascular beds. Hence, the propensity for congenital or acquired disorders to result in local thrombotic pathology is based on the relative contribution of the various hemostatic regulatory pathways in individual vascular beds. The present review highlights the role of local endothelial regulation in the interaction between local and systemic elements that contribute to vascular bed–specific prothrombotic potential. (Circ Res. 2001;89:117-124.)

Key Words: endothelium • thrombosis • hemostasis • coagulation

Hemostasis is the result of interdependent and complex molecular and cellular pathways that govern vascular integrity and rheology. Congenital or acquired alterations in the dynamic balances can result in marked vascular pathophysiology such as bleeding diatheses or hypercoagulability. A striking feature of hypercoagulable conditions is the focal nature of the resultant thrombotic pathology. Indeed, such disorders in hemostasis may be associated with distinct vascular beds, thus implying that the relative combined contribution of individual regulatory pathways may be specific and/or unique to a particular locale in the vasculature. This diversity reflects the interaction of systemic and endothelial components in hemostatic balance, suggesting that heterogeneous regulation of local endothelial cell activity underlies the variable thrombotic potential in different vascular beds.

Clinical Vascular Bed–Specific Hemostatic Pathology

The clinical observations relating to the prothrombotic propensity of various disease syndromes offered the earliest insights into the biological basis of vascular bed–specific hemostatic pathology. Indeed, clinical studies have demonstrated that abnormalities in both protein and cellular hemostatic regulatory elements are associated with specific risks in different vascular beds (Table). For example, it has long been...
**Vascular Bed–Specific Thrombotic Pathology**

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<th>Clinical disorders/associated syndromes</th>
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<table>
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<th>Clinically associated factors</th>
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<td>Fibrinogen</td>
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<td>Plasminogen activator inhibitor-1</td>
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| von Willebrand factor

Appreciated that congenital deficiencies of antithrombin III are associated with an increased risk of deep-vein thrombosis of the lower but not upper limbs.1–5 Similarly, acquired disorders of antithrombin III levels such as through renal losses in nephrotic syndromes are also associated with increased risk of deep venous thrombosis without overtly altering arterial hemostasis. One interesting exception in antithrombin III–associated pathology is a mutation of the heparin binding site of the protease inhibitor. In this case, the abnormal antithrombin III does not bind to heparin and is therefore much less efficient at inhibiting thrombin and other, more proximal enzymes in the coagulation cascade and results in a thrombotic phenotype that involves both arteries and veins.6–9 Alterations in other systemic anticoagulation components also demonstrate vascular bed–specific prothrombotic pathology. Genetic abnormalities in the anticoagulant factors, protein C and protein S, are linked with an increased risk of deep-vein thrombosis of the lower limbs.10,11 Warfarin-induced necrosis of the skin in such individuals, however, is associated with extensive thrombosis of the postcapillary venules and small veins within subcutaneous adipose tissue,12 demonstrating that alterations in the dynamic balance of anticoagulant factors can have a profound role in local hemostatic activity.

Disorders in prothrombotic components are also associated with vascular bed–specific pathology. Antiphospholipid-antibody syndrome is one of the most well-defined acquired forms of prothrombotic pathology. This syndrome demonstrates a propensity toward the formation of clots within particular venous and arterial segments of the vascular tree, including blood vessels of the retina and placenta.13–15 The factor V Leiden mutation is the most common genetic disorder of hemostasis and is predominately associated with venous hemostatic pathology with an increased risk of deep venous thrombosis of the legs and brain, but not with arterial pathology.16,17 Indeed, this mutation does not confer an increased risk of acute myocardial infarction in young women unless they smoke,18 consistent with an increased requirement for additional prothrombotic stimuli to promote thrombosis in the coronary arteries. To this end, unstable coronary events that are caused primarily by thrombotic lesions are not associated with prior preclinical increases in systemic coagulation activity as measured by fibrinopeptide A levels19; in fact, factor VIIa and factor X activation peptide concentrations are inversely related to risk,20 thus indicating that perturbations of local hemostatic pathways predominate the thrombotic pathology in cardiac vascular beds. The risk of myocardial infarction is not, however, without increased thrombotic activity. Indeed, recent studies have demonstrated a correlation between high levels of activated factor XII and the occurrence of coronary arterial thrombotic events,20 demonstrating the potential importance of local hemostasis pathways in governing the activation of systemically derived coagulation factors.

The local vascular bed predisposition to prothrombotic pathology also extends to platelet disorders. Paroxysmal nocturnal hemoglobinuria is associated with an unusually high incidence of macrovascular thrombosis in arterial beds, particularly in the heart and central nervous system.21,22 The microthrombotic lesions characteristic of thrombotic thrombocytopenic purpura are detectable in all organs, with the notable exception of the liver and the lungs.23–25

The biological basis for the local or restricted vascular thrombotic pathology must extend beyond the systemic dysfunction of hemostatic pathways caused by congenital or acquired defects that result in the absence of circulating natural anticoagulants or the presence of activated cell surface membranes. Indeed, alterations in endothelial pathways that mediate the activity of systemically derived cellular and noncellular components may be critical in maintaining vascular bed–specific hemostatic regulation. This review aims to characterize the hemostatic system on the basis of the dynamic interactions and coregulation between its systemic and endothelial components to provide a framework from which to develop a model for understanding the biological basis of vascular bed–specific thrombotic pathology.

**Hemostasis: The Complex Union of Systemic and Local Factors**

The systemic circulation carries critical enzymes and cellular components required for hemostasis. Indeed, the majority of the factors in the coagulation as well as fibrinolytic cascades are generated by the liver and secreted into the bloodstream. Similarly, platelets circulating in the blood throughout the vasculature are central to blood clotting. The local vasculature is primarily composed of endothelial cells and the factors...
and elements derived from these cells. The interaction between the systemic and local pathways provides the necessary actions required to regulate vascular bed–specific hemostatic activity.

Systemic Procoagulation Factors
Clinical analysis of hemostatic potential gave rise to the traditional segregation of the coagulation enzymatic pathways into the extrinsic, intrinsic, and common cascades. These pathways are based on enzymatic studies that have facilitated the comprehensive characterization of the molecular interactions mediating protease activation in vitro as well as the development of clinical anticoagulation therapy monitoring systems. The extrinsic pathway of blood coagulation is initiated when blood is exposed to the subendothelial space. Tissue factor binds to activated factor VII, and the resulting enzyme complex activates factors IX and X of the intrinsic and common coagulation pathways, respectively. Factor IX activated by the tissue factor pathway in turn activates factor X, in a reaction that is greatly accelerated by factor VIII. Once activated, factor Xa converts prothrombin to thrombin (factor IIa) in a reaction that is accelerated by factor Va. In the final step of the coagulation pathway, thrombin cleaves fibrinogen (factor I) to generate fibrin monomers, which then polymerize and link to one another to form a chemically stable clot. This latter reaction includes the activation of factor XIII and its subsequent covalent cross-linking of fibrin polymers. Thrombin also feeds back to activate cofactors VIII and V, thereby regulating the levels of active enzymes in the coagulation mechanism. The intrinsic pathway (defined as a non–factor VIIa cascade) is initiated by activated platelets or the exposure of subendothelial tissue to activate factor IX in the presence of phospholipid and calcium. The enzymatic cascade then leads to the activation of the common coagulation cascade and the subsequent cleavage of fibrinogen and polymerization of fibrin.

Systemic Anticoagulation and Fibrinolytic Factors
The hemostatic cascades have the ability to regulate the level of coagulation enzymes such that a fibrin clot seals injured blood vessels but does not normally permit dissemination of the blood clotting process throughout the vascular system. The potentially explosive nature of this cascade is offset by natural anticoagulant mechanisms. The maintenance of adequate blood flow and the regulation of cell-surface activity limit the local accumulation of activated blood-clotting enzymes and complexes. Antithrombin III is a plasma protein that inhibits the activity of the serine proteases of the intrinsic and common coagulation pathways. In the presence of endothelial cell heparan sulfate, the rate of inactivation is increased by a factor of several thousand. Moreover, in addition to the direct inhibition of coagulation factors, hemostatic activity is suppressed by the retargeting of prothrombotic proteolytic activity to activate enzymatic anticoagulation pathways. Indeed, in the presence of thrombomodulin bound to endothelial cells, thrombin activates protein C, which in turn cleaves activated factors VIII and V. Furthermore, like other reactions in hemostasis, this one is accelerated by a cofactor, in this case protein S. Other pathways also involved in the negative feedback loops of the coagulation system include tissue-factor–pathway inhibitor, which is a lipoprotein-associated plasma protein that forms a quaternary complex with tissue factor and activated factors VII and X, thereby inhibiting the extrinsic coagulation pathway.

In addition to enzymatic mechanisms that inhibit the generation of thrombin and fibrin formation, the systemic hemostatic system has circulating factors that act to break down the fibrin clot. Plasmin is the critical enzyme responsible for the enzymatic degradation of fibrin. The enzyme circulates as a proenzyme, plasminogen, and is activated by tissue-type plasminogen activator and urokinase-type plasminogen activator. In addition, like the regulation of systemic procoagulation factors, the activities of fibrinolytic pathways are governed by the specic enzymatic inhibitor α2-antiplasmin and by the family of plasminogen activator inhibitors.

Platelets: Systemic Cellular Elements
In addition to protein factors, platelets play a vital role as systemic components of the hemostatic system. As described above, platelets are critical in the activation of the intrinsic pathway factors. These highly specialized cellular elements are derived from megakaryocytes in the bone marrow and circulate in the blood. They are activated by an array of stimuli including collagen and other factors in the subendothelial space exposed by disintegration of vasculature architecture as well as by thrombin generated by the enzymatic coagulation cascades. Platelet activation is also mediated through autoaggregatory pathways via release of ADP, thromboxane A2, and serotonin. In addition, activation and aggregation of platelets also provide a cell surface for the assembly of blood-clotting enzyme complexes as described above to further promote prothrombotic pathways.

Endothelial Cells: Local Regulatory Element
A common theme of the systemic elements is that they are regulated by local events in the vasculature. The endothelium provides the specialized lining of the vasculature and is critical in the local regulation of coagulation and fibrinolytic factors as well as platelet activity. Moreover, recent studies using a combination of molecular, genetic, and cellular approaches have begun to elucidate some of the pathways mediating local hemostatic regulation that may be critical in the prothrombotic predisposition of individual vascular beds.

Endothelial Regulation of Systemic Thrombotic Factors
One of the most obvious phenotypic functions of the endothelium is to serve as a physical barrier to constrain the components in the blood to the vascular lumen. In addition to this overt role in vascular integrity, the endothelial cells function as a dynamic blockade of the interaction of systemic coagulation components with subendothelial elements that lead to the activation of the coagulation pathways as described above. Activation/retraction of the endothelial monolayer thereby directly promotes the activation of the clotting cascade.
Endothelial cells also play an active role in the enzymatic regulation of hemostasis. On the anticoagulant side, the endothelium produces heparan sulfate, which increases the kinetics of antithrombin III inhibition of activity of the serine proteases of the intrinsic and common coagulation pathways such that the rate of enzyme inhibition is primarily a function of diffusion rather than the activity of the inhibitor. Endothelial cells also express thrombomodulin on their cell surfaces, which catalyzes thrombin activation of protein C as described above. However, unlike what is known about heparan sulfate, thrombomodulin expression is heterogeneous. For example, endothelial expression of thrombomodulin in the murine aorta is higher in the abdominal than in the thoracic aorta, suggesting that the contribution of the thrombomodulin pathway in the regulation of hemostasis may differ in various vascular beds. Endothelial heterogeneity may also impact on the activation of systemic coagulation factors. Previous studies have demonstrated that von Willebrand factor is predominantly expressed in endothelial cells of the macrovasculature and may underlie differences in the initiation of coagulation cascades in large versus small vessels. Similarly differential endothelial expression of tissue factor may also contribute directly to the activation of coagulation cascades in different vascular beds.

**Endothelial Regulation of Systemic Fibrinolytic Factors**

The endothelium plays a critical role in the regulation of the enzymes in the fibrinolytic cascade. Endothelial cells directly promote the generation of plasmin through the expression of receptors of plasminogen (annexin II) and urokinase, as well as the secretion of tissue-type and urokinase plasminogen activators. However, analogous to vascular bed–specific differences in endothelial pro- and antithrombotic components, the fibrinolytic potential of the endothelium is not uniform. Previous studies have demonstrated that endothelial cells of microvascular beds express 100-fold more tissue-type plasminogen activator as compared with cells of macrovascular beds. Moreover, endothelial cells may also contribute to differential fibrinolytic potential in various vascular beds through the expression of plasminogen activator inhibitors, as previous studies have demonstrated that plasminogen activator inhibitor-1 is expressed at high levels in vascular beds of the murine aorta, heart, and adipose tissue, and at low levels in the liver, adrenal glands, and kidney.

**Endothelial Regulation of Platelet Activity**

In addition to the local control of systemic coagulation and fibrinolytic factors, endothelial cells directly govern the activity of platelets. Endothelial cell synthesis of NO can inhibit platelet activation. The endothelium can also counteract platelet-mediated thrombosis initiated by the release of ADP. EctoADPase, an enzyme on the endothelial surface, catalyzes the degradation of ADP and thereby suppresses additional platelet activation. In addition, endothelial cells also generate prostacyclin, which can directly inhibit the activation of platelets. On the procoagulant side, endothelial von Willebrand factor can directly stimulate platelet activation. Indirectly, endothelialediated stimulation of the coagulation cascade leads to generation of thrombin, which in turn stimulates platelets through cleavage of surface protease receptors.

**Endothelial Heterogeneity Underlying Local Hemostatic Regulation**

The regulation of endothelial cell activity may provide the critical mechanisms underlying the local predisposition of systemic disorders to initiate thrombosis formation in distinct vascular beds. In keeping with Virchow’s triad, the prothrombotic phenotype must arise from local changes in blood flow, disruption of the vascular wall, or vascular bed–restricted alterations in the balance of systemic anticoagulant and procoagulant factors and endothelial regulatory pathways. Such a theory predicts that systemic hemostatic stimuli may produce differential responses in endothelial cells of different vascular beds. Indeed, previous studies have revealed that plasma from patients with thrombotic thrombocytopenic purpura induces a dichotomous effect on endothelial cells from different organs, resulting in decreased prostacyclin and increased apoptosis in endothelial cells of renal and cerebral vessels but not in endothelial cells from the lungs or the liver. The molecular pathways contributing to such a diversity in local endothelial phenotype may be the result of interrelated differences in local vascular blood flow and heterogeneity in endothelial subtype as well as in vascular bed–specific control pathways that may direct local endothelial phenotype subtype activity. Indeed, the distinction between these overlapping regulatory mechanisms is made to provide a framework for characterizing the marked biological complexity in the control of endothelial activity.

**Rheological Regulation of Local Vascular Endothelium**

Local differences in blood flow can contribute to the marked diversity in hemostatic activity in the vasculature. The shear stress produced by hemostatic force can directly induce signaling pathways leading to the expression of a critical set of hemostatic genes including thrombomodulin, tissue-type plasminogen activator, tissue factor, and NO synthase to influence local hemostatic activity. The higher hemodynamic forces in arteries as compared with veins, as well as the increased shear stress on the vasculature distal to bifurcations in blood vessels, may contribute to the differential activation of the underlying endothelium in these vascular beds. Previous studies have also revealed that increases in blood flow lead to upregulation of NO synthase mRNA in the endothelium of the aorta (systemic pressure vascular system) but not in the endothelium of the pulmonary arterial system. Such responses may represent the macro- and microvascular bed–specific adaptive capacity required to maintain hemostatic balance across a range of rheological conditions. Indeed, the relatively large surface area of the microcirculation relative to the macrocirculation accompanied by the low pressure head in this system may necessitate the differential activation of prothrombotic and antithrombotic elements to prevent fibrin deposition. Moreover, changes in cardiac output and local vasomotor tone may directly contribute to
the dynamic prothrombotic predisposition of individual vascular beds.

Vascular Bed Endothelial Cell Subtype Activity
The subtype of endothelial cells represents a second mechanism contributing to the generation of vascular bed–specific phenotypes. Previous research has demonstrated considerable differences in the properties of endothelial cells in microvascular versus macrovascular beds. Endothelial cells derived from arterial, venous, and microcirculatory beds display notable differences in mitotic rates. At a molecular level, endothelial cells demonstrate vascular bed–specific responses to systemic inputs. Endothelial cells from macro- versus microvascular beds exhibit differential growth responses to exogenous factors or stimuli. Studies with thrombin, bradykinin, and vascular endothelial growth factor demonstrate divergent signaling pathways and transport properties of aortic, retinal, and umbilical vein endothelial cells. Similarly, histamine induces differential cAMP responses in cultures of aortic and venous endothelial cells. Moreover, trypsin induces production of prostaglandin I2 in endothelial cells from the aorta but not the pulmonary artery, whereas thrombin increases prostaglandin I2 in venous endothelial cells but not in the arterial endothelium. Endothelial subtype heterogeneity is also present within individual vascular beds as evidenced by the heterogeneous expression of intercellular adhesion molecule-1 (CD54) in endothelial cells of the umbilical vein, suggesting that the association of cellular adhesion molecules with thrombosis may play a critical role in vascular bed–specific hemostatic activity. Indeed, soluble forms of P-selectin have been correlated with both platelet and endothelial activity and more recently have been shown to play a direct role in the procoagulant state. Studies have also demonstrated that cardiac microvascular endothelial CD36 expression may also lack uniformity, suggesting the present distinct subpopulations of endothelial cells in this vascular bed. Indeed, recent studies have demonstrated that cardiac microvascular expression of von Willebrand factor is confined to the subpopulation of endothelial cells bearing platelet-derived growth factor-α receptor that mediates a local endothelial–cardiac myocyte communication pathway (see below). Taken together, these studies demonstrate that endothelial cell subtypes may be critical in the hemostatic pathways of local vascular beds.

Local Endothelial Cell Communication Pathways
Organ-specific or vascular bed–specific endothelial communication represents a third mechanism by which the local endothelium is regulated. Previous studies have demonstrated that expression of plasminogen activator inhibitor type 1 in human endothelial cells is downregulated by conditioned medium obtained from smooth muscle cells of the pulmonary artery but is upregulated by smooth muscle cells isolated from the aorta, umbilical vein, and arteries. Similarly, endothelial cells of the cardiac microvasculature are regulated by a communication with cardiac myocytes. Previous studies demonstrated that a cardiac myocyte–transforming growth factor–β–mediated communication induces the expression of preproendothelin-1 in the microvascular endothelial cells of the murine heart, suggesting that this pathway may control vascular tone and, potentially, platelet activity in the cardiac microcirculation. More recent studies have revealed that a platelet-derived growth factor–cardiac myocyte pathway governs cardiac microvascular endothelial expression of von Willebrand factor, tissue-type plasminogen activator, and endothelial NO synthase. These findings serve to further document the potential importance of endothelial communication with surrounding cell types that may be critical in direct local vascular regulation of hemostatic activity. Alterations in such communication pathways through changes in endothelial cells, endothelial cell subtype, and/or the surrounding cells may lead to significant changes in local hemostatic function.

Experimental Models of Hypercoagulation
The clinical and in vitro studies highlighted above have contributed to the role of the different components in the regulation of hemostatic pathways. Unfortunately, these investigations have not provided significant insight into the mechanisms by which alterations in individual systemic components and local endothelial cells lead to vascular bed–specific prothrombotic pathology. To this end, recent genetic manipulations of the murine genome have offered a unique experimental approach to define the relative contribution of the dynamic interactions of local and systemic pathways on the predisposition of particular beds to acquire vascular pathology.

Murine models have illustrated the apparent dichotomous roles of the ADP regulatory mechanisms in regulation of systemic and local hemostatic pathways. Mice generated with allelic deletion of the ectoADPase gene demonstrate insignificant fibrin deposition in multiple organs in the presence of a relative systemic hypocoagulable state. Moreover, hypoxic stress that potentiates fibrin deposition in the lungs highlights the potential importance of this endothelial enzyme in the hemostatic regulation of the pulmonary vasculature. In vivo genetic models have also provided unique insight into the potential complexity of the enzyme structures that regulate prothrombotic activity in vivo. Indeed, previous studies have demonstrated that administration of recombinant ectoADPase alone results in direct inhibition of platelet function in vivo, suggesting that additional cofactors/enzymes in an ectoADPase-dependent complex on the endothelial cell surface may mediate the regulation of hemostatic activity in the intact vasculature.

Murine genetic studies have also contributed to understanding of the in vivo contributions of the plasminogen activator system components. Mice generated without plasminogen demonstrated fibrin clots in the liver, ovary, lung, colon, and stomach, whereas deletion of the urokinase gene resulted in fibrin deposition in liver, intestine skin, and rectum. Subsequent studies have revealed that deletion of tissue-type plasminogen activator or urokinase-type plasminogen activator results in fibrin in the heart and spleen and lacking both plasminogen activators demonstrate increased fibrin deposition in the heart, spleen, and lungs; however, the
brain and kidneys were completely spared, illustrating the importance of different regulatory pathways in the hemostatic activity of specific vascular beds.

Targeted gene studies in the mouse have also provided the ability to comprehensively study the interrelation between enzymatic activity and vascular bed–specific thrombotic pathology as evidenced in a series of recent studies of the role of thrombomodulin activity in hemostatic regulation. Homozygous deletion of the thrombomodulin gene results in embryonic demise; however, mice homozygous for a point mutation in thrombomodulin that results in poor thrombin binding and little protein C activation maintain a normal life span. In vitro experiments have revealed that this mutant enzyme has 0.1% of the kinetic enzymatic activity of the intact enzyme and thereby allows mice to be generated with various levels of thrombomodulin activity. As expected, depression in enzyme activity led to increases in fibrin deposition in various organ beds, which facilitates the assessment of the relative contribution of the thrombomodulin pathway in regulating local hemostatic pathways. These studies demonstrated that fibrin deposition was directly dependent on the thrombomodulin activity in the cardiac and pulmonary vasculature; however, the lungs were significantly more dependent on thrombomodulin activity as compared with the heart in the prevention of fibrin formation (Figure 1). Indeed, these findings are consistent with the proposed role of altered thrombomodulin activity that may underlie the profound fibrin deposition in the microvasculature of the lung in individuals with primary pulmonary hypertension.

Murine genetic studies have also revealed the role of individual factors in protecting the heart from myocardial infarction. The ability of the heart to maintain hemostasis at lower levels of thrombomodulin activity suggested the relative importance of other anticoagulant or profibrinolytic components such as tissue-type plasminogen activator, which is regulated by the cardiac microvasculature communication. Indeed, mice generated with depressed thrombomodulin activity and tissue-type plasminogen deletion develop spontaneous myocardial infarctions with microvascular thrombosis in the absence of atherosclerosis. Moreover, these studies illustrate the complementary contributions of the thrombomodulin and tissue-type plasminogen pathways in cardiac hemostasis relative the thrombomodulin-dependent regulation in the lung.

Conclusion

The integration of the results of genetic murine studies with clinical and biochemical research provides a unique insight into the relative role of various hemostatic pathways in local vascular beds. Taken together, these findings highlight the critical distinction between systemic activation of the coagulation cascade and the regulation of hemostasis in the local vascular bed through the control of local endothelial activity, as illustrated in Figure 2. The relative contribution of various coagulation and fibrinolytic pathways that are governed by the local endothelium may thereby define the prothrombotic predisposition of different vascular beds. Indeed, such a model predicts that local activation of the coagulation system may represent the actual risk factor(s) for ischemic heart disease rather than induction of systemic hypercoagulability. The results of future genomic research aimed at hemostatic disorders in conjunction with expanded in vitro and in vivo experiments will provide a more comprehensive understanding of the critical systemic-local interactions responsible for vascular bed–specific thrombotic pathology and may provide a foundation for developing approaches for specifically predicting, treating, and/or preventing such disorders.

Acknowledgments

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