Endothelium and Fibrinolysis in Hypertension
Important Facets of a Prothrombotic State?

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Despite the blood vessels in hypertension being exposed to high pressure, the main complications of hypertension (ie, heart attacks and stroke) are paradoxically thrombotic in nature rather than hemorrhagic. Increasing clinical and laboratory evidence is consistent with the concept that hypertension, per se, may confer a prothrombotic or hypercoagulable state, with abnormalities of coagulation, platelets, and the endothelium.1 Indeed, it has long been suggested that the latter organ, with roles in hemostasis and in regulating the NO/endothelin-mediated relaxation and contraction of the blood vessel wall, may be both a target and/or promoter of hypertension and a promoter of thrombosis and, thus, atherosclerosis.2

Other evidence linking the endothelium to atherogenesis is the presence of vasa vasorum in the adventitia and media at a higher density in atherosclerotic tissue, as well as neovascularization and collateral growth bypassing stenotic vascular disease. Such neovascularization reflects the process of angiogenesis, and given these close links, it is no surprise that angiogenesis is yet another important aspect of the pathophysiology of vascular disease, intimately linked with both thrombogenesis and atherogenesis, in a new “vascular triad.”3 For example, the major angiogenic growth factor, vascular endothelial growth factor, is linked with both NO and with a major proinflammatory cytokine, interleukin-6.3 However, skeptics would argue that the clinical (ie, human) evidence does not conclusively show evidence of overt angiogenesis, per se, in conditions such as hypertension, despite (eg) the presence of high levels of factors associated with angiogenesis, such as vascular endothelial growth factor. Thus, we have even proposed that these angiogenic markers do not necessarily translate into new vessel formation but may well reflect disturbances of endothelial integrity in cardiovascular conditions.3

An additional aspect of vascular biology is that sympathetic activation is also related to the pathogenesis of essential hypertension.4 As reviewed by Grassi,5 a hyperadrenergic state is evident in the early hypertensive phases, and sympathetic activation becomes even more evident in stable hypertension and contributes to the maintenance of high blood pressure. The occurrence of such adrenergic activation, both at the cardiac and peripheral vascular levels (ie, sympathetic dysfunction), is closely related to reflex mechanisms (eg, arterial baroreceptor impairment), metabolic factors (insulin resistance), and hormonal agents (angiotensin II and leptin). This adrenergic overdrive can exert various adverse effects on the cardiovascular system, leading to cardiac hypertrophy, vascular hypertrophy, arterial remodeling, and endothelial dysfunction.5 Sympathetic activation is also related to thrombogenesis. As von Känel and Dimsdale6 observe, there are historical reports suggesting the hastening of blood coagulation after intravenous administration of epinephrine, and their systematic review of the literature suggests a dose-dependent stimulation of factor VIII clotting activity, von Willebrand factor antigen, tissue-type plasminogen activator (t-PA), and platelets within a 15- to 40-minute infusion of epinephrine. Coagulation and fibrinolysis molecules are released into circulation by stimulation of the vascular endothelial β-adrenoceptors (most likely β2-receptors), whereas combined α2- and β2-adrenoreceptor–related mechanism(s) are more responsible for platelet activation.6

Given this relationship between sympathetic activation and abnormal coagulation, could sympathetic stimuli influence the endothelium (as reflected by NO availability) and modulate coagulation/fibrinolysis? In the present issue of Hypertension, Gianmarelli et al7 investigate the relationship between adrenergic stimuli and NO in modulating t-PA release from endothelial cells in 58 normotensive and 44 essential hypertensive patients. Their study demonstrates that adrenergic-induced t-PA release is mediated by adrenoreceptors via a mechanism involving the NO pathway, and there is impaired adrenergic-stimulated t-PA release among hypertensive subjects, probably mediated via reduced NO availability. They conclude that this “impaired fibrinolytic activity” might contribute to the increased cardiovascular risk associated with hypertension.

This study raises some intriguing possibilities. Impaired fibrinolytic function, characterized by increased plasminogen activator inhibitor (PAI) type 1 levels and decreased t-PA activity, has been reported in patients with hypertension.1 It is well known that plasma levels of t-PA go up rapidly in response to local adrenergic or muscarinic receptor stimulation, and, in previous studies, such an experimental methodology of assessing adrenergic-tPA release among hypertensive subjects, probably mediated via reduced NO availability. They conclude that this “impaired fibrinolytic activity” might contribute to the increased cardiovascular risk associated with hypertension.

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antigen and activity gives the most complete picture. For example, Otowa et al showed recently that sympathetic nerve activity significantly increased both levels of t-PA and PAI-1 activity, particularly in older subjects, because in the younger subjects t-PA activity tended to increase, whereas PAI-1 activity was unchanged. Of note, t-PA and PAI-1 are both synthesized in the endothelium, but endothelial damage/dysfunction probably results in an imbalance between t-PA and PAI-1, thereby creating a procoagulant surface.

To keep things simple, quantification of plasma levels of t-PA antigen may reflect the endothelium, whereas t-PA activity may reflect fibrinolytic activity. The complex association between these markers, and their intimate relationship to hemostasis and fibrinolysis, may make them less suitable for their use in the assessment of endothelial function, per se. Hence, the conclusion by Giannarelli et al that the impaired adrenergic-stimulated t-PA release among hypertensive subjects reflects an “impaired fibrinolytic activity” might be interpreted differently, as simply reflecting yet another facet of endothelial dysfunction.

Given the intimate relationship between thrombogenesis (coagulation/fibrinolysis) and the endothelium, the precise division may ultimately be difficult to dissect. Furthermore, the role of platelets may complicate the picture, because platelets contain both activator(s) and inhibitor(s) of plasminogen activation by t-PA, and, as a consequence, a balance between activator(s) and inhibitor(s) in platelets may be required for control of the fibrinolytic pathway. Given that abnormalities of platelets are evident in hypertension and may contribute to the prothrombotic state, the endothelium and abnormalities of fibrinolysis in hypertension may simply reflect various facets of a prothrombotic state associated with this condition (Figure).

Where do we go from here? As Giannarelli et al comment, understanding the precise mechanisms underlying stimulated t-PA release could perhaps lead to more specific therapeutic strategies to improve endothelial fibrinolytic function and possibly reduce cardiovascular risk in essential hypertension. Nonetheless, we already have fairly well-validated treatments for hypertension, such as the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, that already show many beneficial effects on the endothelium, fibrinolysis, coagulation, platelets, angiogenesis, and many other facets of vascular biology.

Disclosures

None.

References

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