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. 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.

Other evidence linking the endothelium to atherogenesis is the presence of vasa vasmorum 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.” For example, the major angiogenic growth factor, vascular endothelial growth factor, is linked with both NO and with a major proinflammatory cytokine, interleukin-6. 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.

An additional aspect of vascular biology is that sympathetic activation is also related to the pathogenesis of essential hypertension. As reviewed by Grassi, hyperadrenergic activity, has been reported in patients with hypertension. 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 t-PA release has been used as a tool in measuring endothelial function. However, studies measuring levels of t-PA are hindered by its being bound by PAI-1 so that antigen levels (measuring total t-PA) will differ from activity levels (ie, that t-PA unbound to PAI-1). It has been long suggested that comeasurement of PAI-1 and t-PA...
antigen and activity gives the most complete picture. For example, Otowa et al9 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 al7 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.10 Given that abnormalities of platelets are evident in hypertension and may contribute to the prothrombotic state,1 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 al7 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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