Increased Plasminogen Activator Inhibitor-1 and Vasculopathy
A Reconcilable Paradox
Burton E. Sobel, MD

A Paradox
Altered activities of plasminogen activator (PA) and plasminogen activator inhibitor type-1 (PAI-1) in vessels are associated with atherosclerosis. However, their impacts on the inferred pathogenetic mechanisms seem contradictory. Proteolysis mediated by PAs contributes to vascular smooth muscle migration, neointimalization, and activation of matrix metalloproteinases (MMPs) that precipitate plaque rupture. Conversely, PAI-1 is increased in blood and vessel walls with type 2 diabetes mellitus, yet the incidence of acute coronary syndromes (ACS) precipitated by plaque rupture is extraordinarily high.

Atherogenesis entails the following steps: activation of monocytes/macrophages by oxidized LDL and expression of monocyte chemotactic activating factors such as leukocyte CXCR-2 and its homologs and ligands; their migration into the neointima and elaboration of MMPs; consequent fragmentation of the internal elastic lamina; accumulation of lipid; migration and subsequent proliferation of vascular smooth muscle cells (VSMCs); and proliferation of VSMCs that form largely cellular plaques that can obstruct flow. Until recently, such lesions were thought to account not only for effort-induced clinically stable angina pectoris but also for ACS including unstable angina, Q- and non–Q-wave myocardial infarction (MI), and sudden cardiac death.

Falk and Davies et al identified an important dichotomy. They found that plaques associated with ACS differ strikingly from those typically associated with stable angina by being lipid laden, remarkably acellular, and covered by thin fibrous caps prone to rupture. Activated macrophages in the shoulder regions of such plaques precipitate plaque rupture mediated by activation of MMPs. Rupture precipitates intramural hemorrhage and thrombosis, luminal compression and obstruction, and ACS.

PAs and Migration of VSMCs
Neointimal migration of VSMCs depends on surface expression of PAs. Plasmin generated from plasminogen in the extracellular matrix activates MMPs and facilitates migration. Thus, proteolysis is pivotal in initiation of plaque formation (activation of monocytes/macrophages), migration of VSMCs (surface proteolysis), and rupture of complex plaques precipitating ACS.

This paradigm accounts for the precipitous decrease in incidence of ACS (by 25% to 80%) after lipid lowering despite only trivial diminution of obstruction (0.054% to 2.2%). The dichotomy reflects plaques being rendered more stable by reduction of the ratio of core lipid to cellular elements. The paradigm accounts also for decreased ACS seen with the use of anti-inflammtory, antiplatelet, and anticoagulant agents.

Resolution of the Paradox
One condition underlying ACS, insulin resistance with or without impaired glucose tolerance or frank type 2 diabetes mellitus, is characterized by inhibition of proteolysis. Thus, PAI-1 is increased in blood and in coronary plaques in patients with type 2 diabetes. Insulin increases PAI-1 protein and mRNA in vessel walls and PAI-1 protein in blood. Hyperinsulinemia induced in normal subjects increases blood PAI-1. Although it is obvious that increased PAI-1 can limit fibrinolysis and potentiate thrombosis that precipitates ACS, it is not obvious how increased PAI-1 and decreased proteolysis in vessel walls can exacerbate vasculopathy, because proteolysis is so pivotal in atherogenesis. Furthermore, plasminogen knockout mice exhibit decreased migration of VSMCs after electrical injury to vessels that has been interpreted as indicative of protection against vasculopathy. In addition, in PAI-1–overproducing mice, VSMC migration is attenuated, and VSMC accumulation is reduced at sites of injury.

The conventional wisdom holds that (1) accumulation of VSMCs and formation of a thick, cellular neointima is “bad” (a hallmark of “malignant” atherosclerotic lesions), and (2) inhibition of migration of VSMCs (and subsequent proliferation) is “good.” However, this view may be wrong.

In evolving atheroma, elevation of PAI-1 is marked. PAI-1 is prominent in early fatty lesions in nondiabetic subjects and in complex atheroma known to predispose to ACS in diabetic subjects. As in PAI-1–overproducing mice, the increased PAI-1 should inhibit VSMC migration, subsequent proliferation, and accumulation. However, such inhibition may be bad if it predisposes to formation of acellular plaques. By analogy, inhibition of scar formation makes wound healing “look better” but predisposes to dehiscence; inhibition of granuloma formation with mycobacterial infection; inhibition of granuloma formation with mycobacterial
infection makes the lung "look better" but predisposes to death. Thus, inhibition of VSMC migration may make evolving atheroma look better yet predispose to formation of preponderantly acellular plaques particularly prone to rupture.

In fact, observations in genetically modified mice are consistent with this interpretation. The response to injury is impaired migration of VSMCs and a disproportionate decrease in the ratio of VSMCs to matrix and fibrous tissue. These findings may in fact reflect an impaired response to injury that sets the stage for the thin-walled aneurysms seen rather than protection against vasculopathy. Observations in patients with hyperinsulinemia and type 2 diabetes are consistent with this view. The increased level of PAI-1 in atheroma and in vessel walls appears likely to potentiate formation of atheroma plaques with lipid-laden cores and thin fibrous caps—plaques particularly prone to rupture. This would account for the high incidence of ACS and the adverse response to angioplasty (4-fold increase in 5-year mortality to 35%).

Construing inhibition of migration of VSMCs as deleterious and migration as protective requires a novel perspective. Changing one’s mind-set is analogous, in a sense, to shifting from 1 perceived element to another in an Esher drawing (Figure).

Clinical Implications

If the proposed views are correct, inhibition of augmented vessel-wall PAI-1 expression should lead to favorable changes in composition of atherosclerotic plaques that evolve. Increased degradation and decreased accumulation of matrix and robust migration of VSMCs into developing lesions can be anticipated. Thus, a decreased ratio of lipid to VSMCs that renders plaques less prone to rupture would be expected. Similarly, reduced PAI-1 in vessel walls should decrease the incidence of ACS. We have found that thiazolidinediones (insulin sensitizers) decrease PAI-1 in blood in hyperinsulinemic subjects. Favorable changes in carotid intimal-medial thickness consistent with reduction of lipid content have been observed as well in a preliminary study.

Atherogenesis is multifactorial. Increased PAI-1 may predispose to formation of plaques with high lipid-to-VSMC ratios as a result of decreased VSMC migration. Such plaques are particularly prone to rupture and to precipitate ACS. Thus, suppression of PAI-1 gene expression is an attractive pharmacological target.

References


Increased Plasminogen Activator Inhibitor-1 and Vasculopathy: A Reconcilable Paradox
Burton E. Sobel

Circulation. 1999;99:2496-2498
doi: 10.1161/01.CIR.99.19.2496

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/19/2496

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/