Does Heparin Cofactor II Modulate Atherosclerosis and Restenosis?

Douglas M. Tollefsen, MD, PhD

Heparin cofactor II (HCII) is a plasma protein in search of a physiological function. HCII inactivates thrombin by formation of a stable, bimolecular complex. Detection of these complexes in human plasma suggests that HCII inhibits thrombin in vivo. Sulfated polysaccharides such as heparin and dermatan sulfate interact with HCII and increase the rate of thrombin inhibition more than 1000-fold. HCII is homologous to antithrombin, which inhibits not only thrombin but also factors Xa and IXa when bound to heparan sulfate synthesized by endothelial cells; by this mechanism, antithrombin may prevent thrombosis of intact blood vessels. Mutations in the antithrombin gene that decrease its expression by half are associated with an increased risk of venous thromboembolism. Despite much effort on the part of many investigators, a convincing association between HCII deficiency and venous or arterial thrombosis has not been established.

In animal studies, mice that completely lack HCII develop clots more rapidly in their carotid arteries after oxidative damage to the endothelium than do wild-type mice. This work provides direct evidence that HCII inhibits thrombin in vivo. Two clinical studies, reported in *Circulation* suggest that HCII may help to protect people from in-stent restenosis or carotid artery atherosclerosis.

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gender, HCII remained a negative predictive factor ($r = -0.171; P<0.001$) for carotid atherosclerosis after adjustment for the effects of the other variables. In fact, plasma HCII activity was somewhat more strongly correlated with maximum plaque thickness than was HDL cholesterol ($r = -0.111; P<0.05$).

In the decade after World War II, there was a strong positive correlation between the human birth rate and the number of storks observed to be nesting in the city of Copenhagen. It would have been erroneous to conclude from this statistical fact that storks bring babies. Likewise, one should not jump to the conclusion that HCII directly influences the development of in-stent restenosis or carotid atherosclerosis. Nevertheless, one can imagine scenarios in which inhibition of thrombin by HCII in the vessel wall might delay the development of these pathological lesions.

Stent placement almost certainly triggers thrombin generation by disrupting the endothelium and/or the fibrous cap of an atheromatous plaque, allowing plasma factor VIIa to come in contact with tissue factor in the intima.$^7,8$ The factor VIIa/tissue factor complex then converts factor X to factor Xa, which in combination with factor Va converts prothrombin to thrombin. Thrombin proteolytically converts fibrinogen to fibrin monomers, which polymerize to form a clot, and cleaves G-protein–coupled protease activated receptors (specifically, PAR1 and PAR4) on the platelet membrane to stimulate platelet aggregation and degranulation.$^9$ The earliest histological response to stent placement includes local deposition of fibrin and platelets, providing good evidence for the presence of thrombin in this setting.$^{10}$ Thrombin can also activate PAR1 on nearby endothelial cells.$^9$ In response, the endothelial cells express adhesion molecules on their surface and release a variety of chemokines and other mediators that recruit platelets and leukocytes. Thus, thrombin could play a role in the infiltration of neutrophils, lymphocytes, and macrophages that occurs within the first few days after stent placement. Over the next 2 to 4 weeks, the fibrin and platelets disappear, and restenosis occurs as a result of proliferation of smooth muscle cells and deposition of extracellular matrix in the neointima.$^{10}$ Thrombin may induce smooth muscle cell proliferation both directly, by activation of PAR1 on these cells, and indirectly, by causing platelets to secrete platelet-derived growth factor. Therefore, thrombin could have multiple effects in both the early and late stages of in-stent restenosis.

Several lines of experimental evidence suggest that thrombin participates in formation of the neointima. For example, neointima formation in response to mechanical injury of the carotid artery is less intense in PAR1-null mice than in wild-type mice.$^{11}$ This difference seems to reflect defective thrombin signaling in smooth muscle cells or perhaps endothelial cells, as the platelets of PAR1-null mice remain responsive to thrombin (in contrast to human platelets, mouse platelets express PAR3 and PAR4, but not PAR1). In addition, a synthetic peptide analog that selectively antagonizes PAR1 reduces neointima formation in rats.$^{12}$ Various thrombin-specific inhibitors (eg, hirudin and derivatives thereof) also diminish neointima formation in experimental animals,$^{13}$ but other anticoagulants such as heparin are ineffective. Some of the thrombin generated after vascular injury may remain bound to fibrin or to components of the vessel wall in an active form that is protected from inhibition by circulating antithrombin/heparin complexes but is susceptible to inhibition by HCII/dermatan sulfate.$^{14}$ Infusion of dermatan sulfate, but not heparin, attenuates smooth muscle cell proliferation after carotid injury in rabbits.$^{15}$ The antiproliferative effect of dermatan sulfate is most readily explained by stimulation of HCII to inhibit thrombin, although an HCII-independent mechanism has not been excluded. It is reasonable to speculate that, after stent placement, circulating HCII interacts with dermatan sulfate present in the vessel wall, inhibits thrombin, and thereby attenuates one or more of the reactions that lead to restenosis. Patients with higher levels of HCII may be protected to a greater extent than are those with lower levels.

Many of the thrombin-dependent cellular events that lead to restenosis, including platelet activation, stimulation of endothelial cells to express mediators of inflammation, and proliferation of smooth muscle cells, also occur during development of the atherosclerotic plaque.$^7,8$ Thrombin activity has been detected in the neointima of atherosclerotic lesions with hirudin and chromogenic substrates as probes.$^{16}$ Tissue factor is abundant in atherosclerotic plaques and provides a strong stimulus for thrombin generation during episodes of limited endothelial desquamation or disruption of the microvessels present within the plaque. Such episodes are thought to initiate rapid expansion of the atheroma.$^7$ Heterozygous deficiency of tissue factor pathway inhibitor, which blocks the procoagulant activity of factor VIIa bound to tissue factor, promotes atherosclerosis in apolipoprotein E-null mice.$^{17}$ Experimental observations such as this one support the idea that coagulation and atherogenesis are intimately linked. HCII antigen has been detected in the intima of normal human arteries where it might inhibit thrombin.$^{18}$ Arterial smooth muscle cells synthesize proteoglycans that stimulate the thrombin-HCII reaction and may serve as part of an auto-regulatory mechanism to prevent proliferation of these cells in the intima.$^{19}$ Although dermatan sulfate is more abundant in atherosclerotic plaques than in normal arteries, its structure is altered such that its ability to stimulate HCII is reduced.$^{20}$ Therefore, an HCII-dependent mechanism to limit smooth muscle cell proliferation might be lost during atheroma formation, and higher levels of circulating HCII could provide partial compensation for this loss in some patients.

In conclusion, there is a growing body of evidence that thrombin generation is involved in the pathogenesis of in-stent restenosis and atherosclerosis. As a potent inhibitor of thrombin, HCII may help to down-regulate these processes. Takamori,$^5$ Aihara,$^6$ and their colleagues observed negative correlations between plasma HCII activity and the severity of restenosis and atherosclerosis in their patients. These important findings will provide the basis for future clinical and experimental work to determine if HCII is involved directly in arterial pathology or whether, like the storks of Copenhagen, it is there for some other reason.
References


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