Countervailing Effects on Atherogenesis and Plaque Stability

A Paradoxical Benefit of Hypercoagulability?

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Despite considerable progress in defining the role of hypercoagulable states in venous thromboembolic disease, the contribution of hypercoagulability to arterial vascular disease remains less clear. It is now well established that thrombophilic conditions such as factor V Leiden and the prothrombin G20210A mutation are risk factors for deep vein thrombosis, pulmonary embolism, and other venous thromboembolic events.1 By contrast, these thrombophilic factors have not been found to be clinically important risk factors for arterial thrombotic events such as ischemic stroke or acute coronary syndromes,2-4 despite the fact that arterial thrombosis is a frequent complication of atherosclerosis and plaque rupture.5 A commonly accepted explanation for the markedly different influences of hypercoagulability on venous versus arterial thrombotic events is that thrombosis in the deep veins, which occurs at low shear stress, is mediated primarily by activation of the coagulation cascade, whereas thrombosis in arteries is mediated primarily by activation of platelets under conditions of high shear stress.2 This explanation fits well with the clinical observation that antiplatelet drugs, such as aspirin or clopidogrel, are effective in the prevention of arterial thrombotic events such as ischemic stroke or acute coronary syndromes.2-4

Seehaus et al7 report an intriguing series of observations from murine models that may shed new light on the role of the coagulation system in atherogenesis. A different picture emerged, however, when Seehaus et al measured several histological indicators associated with plaque stability. They found that the atherosclerotic plaques in the hypercoagulable mice had smaller necrotic cores, fewer macrophages, thicker fibrous caps, and a relatively higher content of smooth muscle cells and extracellular matrix deposition. These features are characteristic of enhanced plaque stability.11 Long-term administration (for 20 weeks) of a low–molecular-weight heparin reversed these histological changes. Together, these findings suggest that hypercoagulability may produce countervailing effects on atherogenesis and plaque stability, resulting in larger but more stable atherosclerotic plaques.

Seehaus et al7 also observed that hypercoagulability resulted in enhanced outward vascular remodeling,12 characterized by vascular wall hypertrophy without luminal stenosis. Outward remodeling has been observed previously in hyperlipidemic mice.13 The authors suggest that prevention of stenosis may reflect an additional protective effect of hypercoagulability. It is uncertain, however, whether a relative preservation of the vascular lumen protects an atherosclerotic artery from adverse vascular events. It is probably not the extent of luminal stenosis per se that determines the risk of an acute arterial thromboembolic event, but rather the vulnerability of the plaque to rupture. In fact, in human autopsy series, unstable or ruptured plaques are often observed in vessels with outward remodeling.11

The thrombomodulin and factor V Leiden mutations both produce hypercoagulability by inhibiting the function of the protein C anticoagulant pathway, one with a hypomorphic thrombomodulin mutation8 and one carrying the murine equivalent of the human factor V Leiden mutation.9 They found that ApoE−/− mice with genetic hypercoagulability developed larger atherosclerotic plaques in the aorta and brachiocephalic artery. This finding, which is consistent with an earlier report of accelerated atherogenesis in ApoE−/− mice carrying the factor V mutation,10 suggests that hypercoagulability has a potentiating, detrimental effect on de novo atherogenesis. A different picture emerged, however, when Seehaus et al measured several histological indicators associated with plaque stability. They found that the atherosclerotic plaques in the hypercoagulable mice had smaller necrotic cores, fewer macrophages, thicker fibrous caps, and a relatively higher content of smooth muscle cells and extracellular matrix deposition. These features are characteristic of enhanced plaque stability.11 Long-term administration (for 20 weeks) of a low–molecular-weight heparin reversed these histological changes. Together, these findings suggest that hypercoagulability may produce countervailing effects on atherogenesis and plaque stability, resulting in larger but more stable atherosclerotic plaques.

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The thrombomodulin and factor V Leiden mutations both produce hypercoagulability by inhibiting the function of the protein C anticoagulant pathway. The thrombomodulin mutation limits the production of activated protein C (APC) whereas the factor V Leiden mutation impairs the ability of APC to cleave (and inhibit) factor Va. It is unlikely that the protective effects of hypercoagulability on plaque stability are mediated by decreased APC production or activity, however, because APC has potent antiinflammatory and cytoprotective properties in addition to its anticoagulant effects.14 By contrast, a relative lack of APC function might be expected to result in more inflammatory plaques, with increased macrophage accumulation and larger necrotic
cores. It is more likely that the mechanism of protection by hypercoagulability involves increased generation of thrombin, which is an expected consequence of both the thrombomodulin and factor V Leiden mutations. Thrombin has stimulatory effects on vascular smooth muscle cells and enhances the formation of extracellular matrix.\textsuperscript{15,16} Thrombin also may lead to increased fibrosis, and a larger fibrous cap, by inducing the expression of TGF\(\beta\) by vascular smooth muscle cells.\textsuperscript{17} Further evidence that thrombin may mediate the protective effects of hypercoagulability on plaque stability was obtained by Seehaus et al.\textsuperscript{7} Using cultured endothelial cells and monocytes, they found that thrombin inhibits monocyte transendothelial migration via activation of the PAR-1 thrombin receptor on monocytes. Similar findings have been reported in some,\textsuperscript{18} but not all\textsuperscript{19,20} previous studies of monocyte migration and spreading. Together, these findings suggest that increased thrombin generation may lead to the development of atherosclerotic plaques that are larger but less prone to rupture (see Figure).

What are the potential clinical implications of these findings? If hypercoagulability, through increased thrombin generation, does enhance plaque stability then it may have opposing clinical effects in patients with atherosclerosis. On one hand, hypercoagulability may decrease the likelihood of an acute arterial event caused by plaque rupture. On the other hand, it may increase the thrombotic response to acute vascular injury, leading to a larger thrombus and a more severe ischemic injury. These opposing effects of hypercoagulability may help explain why thrombophilic factors have generally not been found to be associated with arterial vascular outcomes in epidemiological studies.\textsuperscript{2-4} By inference, if hypercoagulability enhances plaque stability then anticoagulation therapy might be expected to lead to plaque destabilization and an increased risk of plaque rupture. In this context, it is noteworthy that anticoagulation therapy is occasionally complicated by “blue toe syndrome,” a rare manifestation of atheroembolization.\textsuperscript{21} Thus, the observations of Seehaus et al\textsuperscript{7} raise several interesting questions regarding the use of anticoagulant drugs in patients prone to atherosclerosis. Before extrapolating these findings to the clinic, however, some important limitations of the murine models must be considered and many additional questions must be answered.

Seehaus et al\textsuperscript{7} used semiquantitative histological criteria to assess plaque stability in the brachiocephalic artery of hyperlipidemic mice. The brachiocephalic artery of ApoE\(^{-/-}\) mice is a reasonably good model of advanced human atherosclerosis,\textsuperscript{22} but nevertheless there are several important differences in plaque histology between humans and murine models\textsuperscript{23} that may limit the conclusions of this study. It also is not clear to what extent the findings of Seehaus et al\textsuperscript{7} may pertain to other hypercoagulable conditions or to different anticoagulant drugs, especially if thrombin is the key mediator of the protective effects of hypercoagulability. Most clinically available anticoagulant drugs, including vitamin K antagonists and heparins, inhibit the coagulation system upstream of thrombin generation. It would be interesting, therefore, to determine the effects on plaque stability of antiplatelet drugs as well as several new classes of antithrombotic drugs that target specific coagulation proteases or receptors (eg, thrombin, factor Xa, or PAR-1).\textsuperscript{24} Like most good research studies, the study by Seehaus et al\textsuperscript{7} raises many more questions than it answers. Before clinicians are tempted to put away their anticoagulants, additional studies will be needed in both animal models and humans to confirm and extend these interesting observations.

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References

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