Commentary

So What Is Critically Lacking with Coronary Atherosclerotic Plaques? Perhaps the Antithrombotic Control

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The role of the vulnerable atherosclerotic coronary plaque in initiating local thrombosis, occlusive or not, lethal or not, but certainly a major source of morbidity, if not mortality, is well recognized. Concepts of pathogenesis have evolved from simple thoughts of coronary stenosis before 1968 to the clear evidence that local thrombosis is the immediate cause. The questions of how the thrombogenic cascade is constructed have also greatly evolved, shifting from the contact pathway of thrombin generation and platelet activation to the current understanding that the cellular protein tissue factor is the major initiating receptor and cofactor for the coagulation (i.e., thrombogenic) cascade, both the extrinsic and intrinsic loops of the protease cascade¹ including recruitment of the formidable platelet accumulation. So much for the rather complex biochemistry reduced to a simple format.

The second issue has concerned how and why this happens in a coronary artery speckled with atherosclerotic lesions, small fatty streaks, larger lesions containing cells and more or less fibrous tissue response, local generation of cytokines, metalloproteases, and subject to shear stress and deformation by the very action of the necessary blood flow and the pulsating deformation of each coronary artery. This issue, really a set of rather complex issues, has been greatly advanced by analysis of the atherosclerotic process and by newer taxonomy of atherosclerotic lesions and plaques.² Plaques are not all the same. There are vast differences in the cellular composition and cellular functions as well as the structure of what is really a family of lesions. The work of many investigators has greatly enlightened us as to the risky structure of some plaques with thin fibrous capsules that could easily be sheared by proteolysis combined with shear stress.³ This leads us to a working conclusion that plaques can rupture: a catastrophic event viewed from a simplistic mechanical point of view. However, predicting which of the many plaques will rupture in the future re-

mains an elusive goal, perhaps one for technologies such as *in vivo* diagnostic imaging.

The third issue leads us to the observation that mechanical rupture and physical occlusion of a coronary artery is probably an unusual event. Rather, a slight disruption of the physical integrity of the overlying endothelium permitting access of plasma proteins to the contents of a plaque seems another likely alternative. Many plaques contain abundant amounts of tissue factor,⁴ which when accessed in a permeable plaque by factor VII and VIIa from plasma, form a bimolecular enzyme that converts factors X and IX from the plasma leak into the fractured plaque to their active protease forms and thus the thrombin generating cascade and local endothelial cell and platelet signaling through the endothelial protease activated receptors (PARs).⁵ The plot now seems so evident. Have we really solved the mystery? Probably not. There are critical questions to be resolved if we are to understand more fully the pathobiology of coronary thrombosis (as well as other forms of thrombotic diseases). Basically, as with all high fidelity biological circuits, there are always critically important negative controlling systems. This is true as well with the hemostatic and thrombogenic pathways.

The story gets even more interesting with two further challenges to elucidate the pathobiology. One issue has been advanced quite nicely by the communication by Laszik et al⁶ in this issue of *The American Journal of Pathology*. The other is the more nebulous issue of a predictive nature, namely which of the many plaques in our coronary arteries is going to be the one to rupture, leak, or fracture? This is the hypothesized vulnerable plaque that at some unknown time in the future will undergo physical loss of integrity and produce the local thrombus. There are a number of hypotheses under in-

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vestigation; however, identification and full characterization remain an unachieved goal.

We find an important advance in the current study by Laszik et al.⁶ They examined the density of key proteins of the antithrombotic control pathways⁷ and control endothelial markers of coronary arteries from the hearts removed from patients undergoing heart transplantation. They observed a significant decrease of the two key controlling receptor proteins of the antithrombotic cascade, namely thrombomodulin and endothelial protein C receptor. These were significantly diminished on the endothelium overlying severe atherosclerotic plaques. This was not the case with coronary artery endothelium from control hearts exhibiting only mild atherosclerosis. Since these two receptors together with plasma protein C and protein S are quite capable of inactivating the thrombotic cascade on a vessel, the decrease of the two essential endothelial surface receptors is a remarkably provocative observation and may explain the greater thrombotic potential of severely atherosclerotic coronary arteries.

This is the first study of this type that indicates that these two cell surface receptors central to the required control inhibition of the thrombotic pathways are relatively diminished in severely atherosclerotic coronary arteries. This introduces the reasonable likelihood that more than just local thrombin generation is essential to

generate local coronary thrombi. Perhaps more than physical disruption or leakage of a plaque is required. Perhaps the diminished antithrombotic environment is also a significant contributor and may even be of potential utility in *in vivo* imaging of what may be the vulnerable atherosclerotic plaque.

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