Editorial

A Simple Experiment and a Weakening Paradigm
The Contribution of Blood to Propensity for Thrombus Formation

Yale Nemerson

For many years, arterial thrombosis was considered a result of vascular injury combined with a “normal” response of circulating coagulation factors and formed elements. Indeed, the original articles describing tissue factor in atherosclerotic lesions implied that rupture or erosion of the plaque that results in contact of the circulating blood with plaque-bound tissue factor is sufficient to result in thrombus formation. These formulations ignore the fact that thrombi have been observed to occlude an artery within minutes of formation. These formulations ignore the fact that thrombi have been observed to occlude an artery within minutes of vascular perturbations. In retrospect, the role assigned to lesion-bound tissue factor is not physically realistic. The implied mechanism of thrombus growth is that surface-bound tissue factor rapidly binds circulating factor VII/VIIa, thereby forming the catalytic complex that proteolytically activates factors IX and X, thereby generating procoagulant intermediates that lead to thrombin production. This necessarily involves the diffusion of these intermediates from surface-bound tissue factor to platelets, where they form the catalytic complexes that directly generate thrombin from prothrombin. While on a microscopic level, these events are certainly accurate; occlusive thrombi are macroscopic structures that can rapidly grow to \( \approx 3 \) mm. Consider that a protein of \( \approx 50 \) kDa, typical of procoagulant intermediates, would, on average, take some 3 hours to diffuse 1 mm through water. In reality, the diffusion would be obstructed by adherent platelets and fibrin, which would reduce further the effective diffusion rate of these proteins.

See pages 1495

This reasoning led us to examine more closely the participation of blood components in thrombus propagation. Using ex vivo and in vitro techniques, we were able to demonstrate the participation of blood-borne tissue factor in the formation of thrombi on collagen-coated surfaces and on arterial media. The article by Karnicki and colleagues significantly expands the previous results inasmuch as they performed a simple but revealing quantitative experiment. The fundamental question they addressed is the relative contribution of blood elements and arterial surfaces to formation of thrombi on arterial segments perfused with heparinized blood. The experimental design enabled these investigators to conclude that, in an all-porine system, the thrombotic mass was more regulated by the blood than by the particular arterial segment used. The experiments were straightforward: blood was obtained from 25 pigs and perfused over arterial segments derived from a single donor aorta. The obverse experiment in which blood derived from 8 different donors was perfused over segments obtained from 12 donors was also performed. Importantly, the thrombotic mass was much more influenced by the blood as compared with the arterial wall.

This interesting and important result clearly indicates the importance of circulating elements in thrombogenesis. Thus, the speculations arising from the identification of circulating tissue factor-containing microparticles and elevated levels of tissue factor antigen noted in patients with acute coronary syndromes now has experimental verification. The mechanism underlying this phenomenon has yet to be clearly elucidated. Karnicki et al unexpectedly found that thrombus mass correlated with the lymphocyte count. Although the leukocyte count has been suggested as a risk factor for myocardial infarction, the current data could be explained by an unknown mechanism, even viral infection, as suggested by these authors. Whatever the explanation, these studies warrant a considerable effort to establish the way in which blood regulates thrombus growth. While porcine thrombosis resembles the human condition, we note the obvious differences between pigs and man.

References
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