Letter to the Editor

Neointimal Cracks (Plaque Rupture?) and Thrombosis in Wrapped Arteries Without Flow

Erling Falk, Stephen M. Schwartz, Zorina S. Galis, Michael E. Rosenfeld

The Editor’s pick for the June 2006 issue of Arteriosclerosis, Thrombosis, and Vascular Biology was the article by Sasaki et al1 entitled “A Simple Method of Plaque Rupture Induction in Apolipoprotein E–Deficient Mice.” The key term in this title is “plaque rupture.” The article was accompanied by a supportive editorial by Jackson.2 We would like to suggest that the enthusiasm for this experiment as a model for plaque rupture needs to be moderated by a better understanding of the model itself and of human plaque rupture.

In 1997, Lindner and coworkers described that flow cessation induced by ligation of the common carotid artery (CCA) near its bifurcation led to constrictive vascular remodeling and neointima formation in mice within 4 weeks.3,4 Flow cessation was followed by loss of medial smooth muscle cells and early recruitment of leukocytes that infiltrated the developing neointima, media, and adventitia during the first week. Focal endothelial detachment with subendothelial accumulation of erythrocytes were also observed, but otherwise the endothelium appeared intact and thrombus was not seen except for the most distal part of the artery near the ligature. However, if the endothelium was removed before ligation, an occluding thrombus formed over the entire length of the carotid artery.3 Later, flow cessation was used to accelerate the formation of macrophage-rich lesions in apoE-deficient mice, and the role of macrophages in expansive arterial remodeling was described.5

Moroi et al introduced in 1998 another mouse model of neointima formation, induced by placing a nonconstrictive polyethylene cuff around the femoral artery.5 The mechanism of neointima formation within a nonconstrictive cuff is not known but localized hypoxia could play a pathogenetic role. The endothelium appeared intact with inflammatory cells infiltrating the arterial wall.6

Then, in 2004, Sasaki et al7 combined these two models and reported that simultaneous ligation and nonconstrictive cuffing of normal CCA in C57BL mice induced site-specific endothelial damage and disruption, exposure of subendothelial tissue, and clotting of the stagnant blood in the lumen, leading to gradual thrombotic occlusion of the cuffed segment within 7 days (subacute thrombosis). The new observation just reported by Sasaki et al1 is that the same happens when the nonconstrictive cuff is placed around a ligated CCA that already has a neointima in apoE-deficient mice. Under this condition the neointima becomes disrupted (called “plaque rupture”), and the stagnant blood within the cuff clots. In both Sasaki models, the nourishment of the arterial wall was first compromised by stopping the flow of blood in the lumen (by ligation) and subsequently the alternative oxygen supply via vasa vasorum was eliminated (by perivascular cuffing). This double hit must lead to severe site-specific hypoxia and probably ischemic necrosis, explaining the “abundant accumulation of neutrophils” observed after placement of the cuff. Although it is true, as mentioned in the article,1 that neutrophils may also be seen in ruptured human plaques, they are usually scarce and, if present, generally assumed to be a consequence rather than a cause of plaque rupture.

At least to the authors of this letter, there is no obvious reason to suggest that the mechanisms underlying neointima breakdown in the Sasaki model recapitulate the processes occurring when the fibrous cap over a lipid-rich necrotic core breaks down and rupture. Furthermore, also the processes leading to thrombotic occlusion of the artery are very unlike those responsible for thrombosis over a ruptured human plaque. In plaque rupture, a necrotic core is, by definition, exposed to the blood via a structural defect in the overlying fibrous cap.8,9 Under the rapid flow conditions that prevail in arteries, exposure of the necrotic core is followed by platelet adhesion, activation, and aggregation that may lead to the formation of an occlusive platelet-rich thrombus.10 None of these key features was modeled by cuffing of ligated arteries. Blood stagnation with clotting occurred consistently in both normal7 and diseased arteries,1 independent of the presence of neointima or plaque.

In summary, Sasaki et al1 as well as the author of the Editorial2 use the terms “plaque rupture” and “fibrous cap” without defining them, and, in particular, the presence of a necrotic core is not mentioned and thus not required. It is apt to create confusion rather than insight and understanding when the term plaque rupture is used for a “cracked” murine neointima that lacks the key features required to diagnose a ruptured plaque in humans: a necrotic core and a torn cap. Thus, the relevance of this murine model to human plaque rupture is not at all clear.

Disclosures

None.
References


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