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

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In Response:
The criticism of Falk et al is based on the lack of evidence of consecutive events in the Sasaki model: plaque breakdown first, then thrombosis formation. As cited by Falk et al, we have previously demonstrated that the simultaneous treatment of ligation and cuff placement in the mouse carotid artery induced occlusive thrombosis which was accompanied with endothelial cell damage in wild-type mice.2 Falk et al may speculate that thrombus formation in our new rupture model was also mediated through the combined application-induced endothelial damage but not through plaque breakdown, or that plaque disruption and thrombus formation may occur independently. We cannot neglect the possibility that plaque disruption (rupture) may not always be necessary for occlusive thrombus formation in the Sasaki model, although we clearly demonstrated the association of neointima cracks with the thrombus formation. To demonstrate the direct relationship between plaque breakdown and thrombus formation, a careful time course study is needed. However, it is very difficult to clarify the time course of plaque disruption and thrombosis formation, because these two events seem to generate at almost the same time. Fibrous cap, which was stained with smooth muscle cell-marker, was detected in the most of the neointima lesions, and cracks were observed at the fibrous cap region, although there was no necrotic core in the lesions of Sasaki model.1 Nevertheless, we believe that our model is still useful for investigating the pathophysiological mechanisms underlying the development of the vulnerable lesion and plaque rupture of humans, because this model represents similar features observed during the process of human plaque rupture: a reduction of collagen content, the presence of matrix metalloproteinases, an increase in apoptotic cells and inflammatory cells in the plaque lesions before the thrombosis formation, followed by neointima cracks and thrombotic occlusion of the artery at the site of the presumed rupture. These events observed in the Sasaki model appear to be analogous to the events in some parts of human plaque rupture. Obviously, this model does not completely reproduce human plaque rupture, the final event in a long and complex pathophysiological process. However, we should take advantage of beneficial parts in this incomplete model, and should also avoid rejecting animal models simply because they do not generate human-like lesions, as described in the editorial by Jackson.3

Finally, we believe that the plaque vulnerability and rupture in the Sasaki model partially overlap with human disease, and improve several disadvantages in previous models of plaque rupture. This model can be used as a useful model of some aspects of human plaque rupture until an animal model with ideal features of human plaque rupture without the need for artificial manipulations is developed.4

Disclosures
None.

References
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