Intraplaque Hemorrhage, RBC-Derived Cholesterol, and Plaque Progression

Time to Move From Conjecture to Evidence?

The interesting study by Sun et al. (1) in a recent issue of iJACC adds important new insights into the role of intraplaque hemorrhage (IPH) in the natural history of carotid atherosclerosis. Serial magnetic resonance imaging (MRI) over an extended period of observation demonstrated that plaque growth after the occurrence of IPH was on average higher compared with the period before IPH (1). Notably, however, the rate of individual plaque growth differed substantially after the occurrence of IPH; some plaques actually showed regression despite evidence of new IPH, as shown in Figure 4 of Sun et al. (1). Thus, this study strongly links IPH to accelerated atherosclerosis, but it also raises a key issue: detection of IPH alone may be a suboptimal predictor of the exact rate and magnitude of subsequent plaque growth. Therefore, identification of other factors that modulate the proatherogenic effect of IPH might enhance the potential of MRI to accurately predict which lesions with IPH will exhibit most pronounced and rapid growth. Based on the pathobiological sequelae of IPH (2), we suggest that differences in the cholesterol contents of erythrocyte membranes (CEM) are very likely to account, at least in part, for the observed differential plaque growth after IPH (1).

The driving mechanisms of plaque progression and the main source of cholesterol that is accumulated in the developing plaque differ fundamentally in lesions without versus those with IPH. In lesions without IPH, cholesterol in the plaque is derived mainly from circulating blood lipoproteins; hence, higher blood cholesterol levels amplify the proatherogenic stimulus of adverse local hemodynamics, which is a major driving force of focal plaque development in this setting (3). In contrast, in lesions with IPH extravasated erythrocytes contain abundant free cholesterol that is absorbed into the necrotic core and is conjectured to contribute centrally to plaque enlargement (2). Accordingly, in lesions with IPH, it seems highly plausible that increasing levels of CEM might amplify the proatherogenic stimulus of IPH per se.

Of clinical importance, the CEM can be measured in the clinic (4,5) and is positively related to coronary plaque burden (4) and plaque instability (5). We hereby propose that the combination of CEM measurement with serial MRI may substantiate our current understanding of the role of IPH in plaque biology and, consequently, may enhance risk-stratification of patients with evidence of IPH. First, a finding of greatest plaque progression after IPH in patients with higher compared with those with lower CEM levels would lend definitive mechanistic support to the long-standing
(yet still unproven) conjecture deriving from pathological studies that erythrocytes are actively implicated in plaque growth after IPH (2). Second, and clinically highly relevant, a combined approach of CEM measurement and serial MRI of the carotid arteries might allow for early identification of patients with IPH who are at highest risk of accelerated plaque growth, and might thus optimize risk-tailored management to avert adverse clinical events. Third, considering that statins effectively decrease CEM (5), differences in IPH-triggered plaque progression in patients treated with different statin regimens (1) might be evaluated on the basis of the CEM-lowering potential of statins.

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REFERENCES