Intraplaque Hemorrhage: An Imaging Marker for Atherosclerotic Plaque Destabilization?

Gerard Pasterkamp, A.F.W. van der Steen

Luminal thrombosis by rupture of the vulnerable atherosclerotic plaque is considered the main pathological substrate of the acute cerebral and coronary syndrome. The traditional definition of the vulnerable plaque has been based on cross-sectional postmortem observations and is reflected by a thin capped atheromatous lesion hiding different types of inflammatory cells that degrade the fibrous tissue. More recently the role of intraplaque hemorrhage (IPH) in atherosclerotic disease progression has gained serious interest. IPHs are caused by neocapillary rupture and relate to angiogenesis from the adventitia toward the plaque. The density of neovessel formation is positively correlated with the extent of necrotic core formation and inflammatory infiltrates, suggesting that vessel formation appears to be linked to the evolution of atherosclerosis from early stage to a complicated lesion. The clinical and biological importance of IPHs has long been neglected, because the majority of biological studies focused on lipid metabolism and the inflammatory responses that are evident in atherosclerotic disease initiation and progression. The presence of intraplaque extravasation or bleeding is no longer considered an innocent bystander but regarded as a feature that contributes to local lipid deposition and acts as a source for proinflammatory responses. It has been shown that lipid-rich lesions reveal costaining for Glycophorin A, a marker for red blood cell membranes. In fact, the membranes of the erythrocytes may be a cellular substrate for atheromatous core formation. About 40% of the weight of the erythrocyte is composed of lipid. Free cholesterol present in the necrotic core may originate from the red cell membrane, which is 1.5 to 2.0 times richer in cholesterol than any other cell, which could explain the consistently observed colocalization of Glycophorin A and lipid in necrotic cores. The membrane of the red blood cell can also bind to macrophage scavenger receptors and subsequently initiate an inflammatory response. In another study in human atherosclerotic plaques it was shown that endothelial junctions may become leaky by which IPH is more likely to occur.

IPH and neovascularization in the carotid arterial wall can be visualized noninvasively. This makes these plaque features interesting candidates as surrogate markers for progression of atherosclerotic plaques and subsequent destabilization of the patient. In a clinical follow-up study it has been demonstrated that MRI-documented IPHs are associated with accelerated plaque progression and cerebrovascular events, whereas plaques without IPH did not progress. The visualization and quantification of the vasa vasorum in atherosclerotic plaques, which is considered to be the source of plaque destabilizing intraplaque bleeding, and the ability to follow their progression using contrast-enhanced ultrasound imaging is another emerging challenge. Current approaches include contrast-enhanced Intravascular UltraSound for the coronary bed (Figure), and contrast-enhanced noninvasive ultrasound for the carotid arteries. This could become of interest because vaso vasorum may be altered in response to plaque stabilizing compounds.

More recently we observed in the Athero-Express study that locally observed IPHs in the carotid arteries are predictive for events in other vascular territories. A similar relationship with future events was observed for the density of neovessels within the local atherosclerotic lesion. This study raised the concept that the degree of plaque vascularization and bleeding in 1 vascular site may reflect the degree of stability of atherosclerotic lesions at other vascular sites and further support the idea that IPH and plaque vascularization could act as a target for noninvasive imaging.

In the current issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Turce et al report a study on the examinations of the associations of IPH with established risk factors for stroke. They considered that the imaging of this plaque feature in prediction studies would not have added value if it would simply reflect another more easily recognized risk determinant of stroke. They executed an MRI study in 234 patients and associated the presence of IPH with clinical presentation and other risk factors for development of stroke. The authors observed a quite consistent association with the degree of stenosis, and in symptomatic patients they noticed a higher prevalence of IPH in patients with more severe clinical presentation (stroke versus TIA/amusouros fugax). In addition, a short delay between the ischemic event and the imaging procedure was associated with a higher incidence of IPH. The data confirm the relation between the presence of IPH and the occurrence of a clinical cerebral event and shows that this relationship is not likely to be confounded by traditional risk factors like diabetes, smoking, hypertension, or body mass index. However, some limitations of this study merit careful consideration.

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reflect the consequence of an event. In addition, although the relationships of IPH with time since last event and clinical presentation are of interest, these parameters cannot be taken into account in a prediction model because they can only be assessed retrospectively.

The study by Turc et al further supports the relevance of IPH in the etiology of atherosclerotic disease progression in patients suffering from carotid artery stenosis. In addition, it confirms previous observations that noninvasive imaging of IPH can gain value as a surrogate measure of future progression of atherosclerotic disease. MRI is now being considered as the noninvasive imaging modality of first choice to visualize IPH. However, we have to appreciate that validation studies that reveal the positive and negative predictive values for detection of IPH using MRI are still limited and that differentiation between lipid necrotic core and IPH may be difficult. The application of high resolution human MRI scanners up to 7T may further improve resolution and discriminative power of different plaque components.

References

**Figure.** Contrast enhanced intravascular ultrasound image of vasa vasorum in an atherosclerotic rabbit aorta (8). The white ring around the catheter (C) is contrast agents against the endothelium. The bright dots around it reflect the presence of ultrasound contrast agents in the vasa vasorum. The tissue is invisible due to the contrast imaging mode.
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