ISSN 1936-878X/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2009.09.009

EDITORIAL COMMENT

Intraplaque Hemorrhage as a Stimulator of Episodic Growth of Advanced, But Nonsymptomatic Atherosclerotic Lesions

Bridging the Gap*

Mat J. Daemen, MD, PhD,† Marianne Eline Kooi, PhD‡

Maastricht, the Netherlands

Both cross-sectional histological studies of human atherosclerotic specimens and a plethora of studies in animal models have provided the current framework for the pathogenesis of atherosclerosis. One major drawback of the current hypotheses is the paucity of longitudinal observations in humans on the natural history of atherosclerosis. Noninvasive imaging studies of human atherosclerosis are able to bridge the gap between cross-sectional pathology observations, animal studies, and longitudinal observations in humans.

See page 1381

In this issue of *iJACC*, Underhill et al. (1) followed for 18 months the development of atherosclerosis in the carotid artery of 67 nonsymptomatic patients with 16% to 49% stenosis who were referred because of a cervical bruit or because they were scheduled for coronary bypass graft or lower extremity bypass. They identified intraplaque hemorrhage (IPH), systolic blood pressure, and statins as the determinants of a change in plaque burden.

IPH as a source of intraplaque growth. Although only 12 (18%) of 67 patients showed evidence of IPH, the presence of IPH was associated with a reduction in lumen volume and an increase in plaque volume, without outward remodeling of the vessel.

The observations that only 18% of the subjects had IPH and that no subjects developed IPH in the 18-month period are intriguing because they suggest that IPH does not occur very often in nonsymptomatic carotid plaques, and if it does, it only occurs in a subgroup of plaques and/or patients.

It also suggests that if IPH occurs, it has potent, long-standing, and stimulatory effects on plaque growth. This plaque growth stimulatory effect is most likely due to the response of the plaque to the presence of erythrocytes and possibly fibrin, which will evoke a classic wound-healing response in the plaque, resulting in the deposition of first loosely oriented and later more mature and cross-linked intraplaque collagens and the formation of new intraplaque vessels. Indeed, cholesterol-rich erythrocytes do attract macrophages into the plaque, leading to phagocytosis of cholesterol-rich erythrocytes, hemoglobin release, and iron deposition. The resulting highly reactive milieu in the plaque forms the base for the wound-healing response and an increase in plaque volume. Erythrocyte phagocytosis does indeed occur in atherosclerotic plaques (2), but is dysfunctional in advanced atherosclerosis and may be limited in capacity.

The observations that IPH remained detectable in the same plaque even after 18 months indicates that either IPH does not resolve very rapidly or that IPH recurs in the same plaque, as suggested by Takaya et al. (3). Evaluation of the age and volume of the IPH is essential to discriminate new from existing IPH, but was not provided. The apparent observation that IPH does not resolve rapidly or does not resolve at all suggests that, in addition to dysfunctional erythrocyte phagocytosis, a normal thrombotic sequence does not occur or inadequately

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Departments of †Pathology and ‡Radiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, the Netherlands.

occurs. One possibility is that plaques with IPH contain high amounts of thrombolytic factors, which may prevent thrombus formation. Molecular imaging is necessary to report on fibrin deposition and/or thrombus formation, which is indeed possible, mainly in the pre-clinical phase (4,5).

Intraplaque microvessels, which originate from the adventitia, are candidate entry sites of erythrocytes. Hypoxia-dependent and -independent molecular mechanisms of plaque microvessel formation have been identified (6). Recently, Sluimer et al. (7) demonstrated evidence of leaky and dysfunctional plaque microvessels with altered endothelial–endothelial junctions and a low mural cell coverage. Because these intraplaque microvessels were spatially linked to monocytes and erythrocytes, they may indeed function as entry sites of plaque constituents and provide a novel source for intraplaque inflammation and hemorrhage.

One important issue is whether the identification of hemorrhage on multisequence magnetic resonance imaging (MRI) does indeed reflect true IPH. Because of obvious reasons, the findings in the present study (1) are not substantiated by histology. Several groups have presented data that show that the presence of IPH can be established with MRI (8–10). The correlation between volumetric measurements of hemorrhage on MRI and histology was reported to be moderate to strong (9), whereas the age of IPH cannot be measured reproducibly (10). Although we have always thought that IPH was a feature of very advanced plaques (and thus involving symptomatic patients), the findings in the present study (1) indicate that a substantial fraction of these asymptomatic patients do show evidence of IPH. The data also indicate that IPH could represent an important accelerator of plaque growth, even at a stage at which an advanced plaque has developed but has not produced clinical symptoms. Note that although by definition lumen volume was still substantial in these asymptomatic patients, plaque volume was also substantial and plaques were advanced because 58% of the plaques measured had a lipid-rich necrotic core, albeit with a limited volume of 80 mm^3, representing only 15% to 25% of the total plaque volume. Thus, the real novelty of the findings is not that IPH does occur in advanced lesions and that its frequency increases with an increase in stenosis (11), but that IPH does occur in advanced lesions of asymptomatic patients. Unfortunately, other assumed key parameters of the risk of plaque rupture such as fibrous cap thickness and, as discussed earlier, the presence of a thrombus, were not measured.

Assuming that IPH is a major driver of plaque growth (3), even in asymptomatic patients, the question arises whether asymptomatic patients with advanced lesions and specific features such as IPH need to be treated because these lesions have a higher chance to progress to symptomatic lesions and ultimately to rupture. Therapeutic options are, however, limited. Adequate statin treatment and blood pressure control are evident. Indeed, also in this study (1), atherosclerosis did not progress in the patients treated with statins, whereas total wall volume increased 22 mm^3/year in the 24 patients who were not taking statins, which represents a relative increase of 3%. Hypertension was also associated with an increase in wall volume.

Whether plaque microvessels are a suitable target to reduce plaque growth and possible plaque inflammation is currently unknown. The recent findings that these plaque microvessels are rather immature (7) suggests that stimulation of plaque microvessel maturation might be a better target than a simple reduction in the number of microvessels, which may increase the hypoxia in the plaque and thereby increase the size of the necrotic core.

How to progress? Although this study (1) does reveal that IPH contributes to plaque progression, even in asymptomatic lesions, it does have limitations. One limitation is the small sample size of only 67 patients, the majority of whom were scheduled for either coronary or peripheral bypass grafting, which may have introduced a selection bias. A second limitation is that the data were obtained and analyzed at 1 center and the follow-up time was only 18 months, which may seem long, but represents only a fraction of the lifetime of an atherosclerotic lesion, which takes decades to mature. Because it was technically impossible to measure the IPH volume, the IPH group was mixed, including lesions with large and small IPH. In addition, growth or regression and location and age of the IPH were not evaluated. The lack of cholesterol levels is a serious omission, and readers must be aware that these measurements were performed in the carotid artery, which may not yield the same results as the coronary artery.

However, now that we know that IPH (and possibly other key parameters of the risk of plaque rupture) is present in a subgroup of even asymptomatic patients and remains detectable for at least 18 months, we need to establish whether other key parameters of the risk of rupture are also present in these lesions and whether this subset of plaques also

increases the risk of the development of a stroke, as was recently suggested by Altaf et al. (12).

Indeed, noninvasive imaging of at least the carotid artery and in the near future possibly also of the coronary artery (13) starts to bridge the gap between our concepts based on cross-sectional histological observations and the real natural history of an atherosclerotic plaque. This opens the possibility of really determining the risk of rupture of an individual atherosclerotic plaque, even when it is still asymptomatic.

Reprint requests and correspondence: Dr. Mat J. Daemen, Department of Pathology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Peter Debyelaan 25, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands. *E-mail: Mat.Daemen@path.unimaas.nl.*

REFERENCES

1. Underhill HR, Yuan C, Yarnykh VL, et al. Arterial remodeling in the subclinical carotid artery disease. J Am Coll Cardiol Img 2009;2:1381–9.
2. Schrijvers DM, De Meyer GR, Kockx MM, Herman AG, Martinet W. Phagocytosis of apoptotic cells by macrophages is impaired in atherosclerosis. Arterioscler Thromb Vasc Biol 2005;25:1256–61.
3. Takaya N, Yuan C, Chu B, et al. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. Circulation 2005;111:2768–75.
4. Spuentrup E, Botnar RM, Wiethoff AJ, et al. MR imaging of thrombi using EP-2104R, a fibrin-specific contrast agent: initial results in patients. Eur Radiol 2008;18:1995–2005.
5. Miserus RJ, Herias MV, Prinzen L, et al. Molecular MRI of early thrombus formation using a bimodal alpha2-antiplasmin-based contrast agent. J Am Coll Cardiol Img 2009;2:987–96.
6. Sluimer JC, Gasc JM, van Wanroij JL, et al. Hypoxia, hypoxia-inducible transcription factor, and macrophages in human atherosclerotic plaques are correlated with intraplaque angiogenesis. J Am Coll Cardiol 2008;51:1258–65.
7. Sluimer JC, Kolodgie FD, Bijnens AP, et al. Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions: relevance of compromised structural integrity for intraplaque microvascular leakage. J Am Coll Cardiol 2009;53:1517–27.
8. Cappendijk VC, Cleutjens K, Heeneman S, et al. In vivo detection of hemorrhage in human atherosclerotic plaques with magnetic resonance imaging. J Magn Reson Imaging 2004;20:105–10.
9. Saam T, Ferguson MS, Yarnykh VL, et al. Quantitative evaluation of carotid plaque composition by in vivo MRI. Arterioscler Thromb Vasc Biol 2005;25:234–9.
10. Chu B, Kampschulte A, Ferguson MS, et al. Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. Stroke 2004;35:1079–84.
11. Saam T, Underhill HR, Chu B, et al. Prevalence of American Heart Association type VI carotid atherosclerotic lesions identified by magnetic resonance imaging for different levels of stenosis as measured by duplex ultrasound. J Am Coll Cardiol 2008;51:1014–21.
12. Altaf N, Daniels L, Morgan PS, et al. Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. J Vasc Surg 2008;47:337–42.
13. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49–57.

Key Words: atherosclerosis ■ imaging ■ risk stratification.