1078 Carotid Plaque Formation and Stability

Monday, March 30, 1998, 3:00 p.m.–5:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: 4:00 p.m.–5:00 p.m.

1078-47 Influence of Cellular Components on Carotid Plaque Rupture

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Background: In spite of the frequency of carotid plaque rupture (CPR), few attempts have been made to characterize its pathogenesis. The cellular and vascular components of 174 surgically excised carotid endarterectomies were studied in order to obtain information about CPR.

Methods: The specimens were serially sliced, aside from classical histological stainings, immunophenotyping of cells was performed with monoclonal antibodies in single and double stainings.

Results: CPR were found in 91/174 cases (52%); 19 associated to thrombosis (THR) (11%), 38 with intraplaque hemorrhage (IPH) (22%) and 31 with THR+IPH (18%). The fibrous cap at the site of the CPR showed an eroded surface with loss of the endothelial lining; in the remaining surfaces a continuous, non-damaged row of endothelial cells CD31+ and CD34+ was observed. The fibrous cap at the site of erosion was attenuated and the characterization of the cells showed in 76/91 (83.5%) 2/3 of macrophages (CD68+) and 1/3 of T-lymphocytes (CD45RO+) and smooth muscle cells (HHF35+). A close interaction between macrophages and capillaries, and macrophages and T-cells was observed. The lipid cores could be depicted as avascular or mild vascularized, with scarce neoformed vessels stained with CD34 and CD31. No highly vascularized cores were observed. In non-ruptured plaques only 37/83 (44.5%) showed a mononuclear infiltrate in the fibrous cap ($p < 0.0001$; Fisher test).

Conclusion: CPR is characterized by macrophagic infiltration of attenuated caps and by the direct apposition of T-lymphocytes to macrophages. This suggests a cell-to-cell interaction, which results in an inflammatory process, cap weakening and CPR.

1078-48 Fibroblast Growth Factor Receptor Expression and its Relation to Smooth Muscle Cell Differentiation and Apoptosis in Human Carotid Plaques

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Background: Vascular growth factors and their receptors, i.e. Fibroblast Growth Factor Receptor (FGF-R), are considered to be involved in carotid plaque formation. They are putatively responsible for smooth muscle cell (SMC) proliferation, dedifferentiation and apoptosis.

Methods: We analyzed 26 human carotid plaques removed by surgery, using immunohistochemistry (TUNEL test to detect fragmented DNA indicating apoptosis), transmission electron microscopy (TEM) and morphometric evaluation.

Results: Our data show a mean intimal cell density of 1013 ± 475 cells/mm^2 (x ± SD; n = 26). The 16 densest lesions showed cell-bound signals of FGF-R at a threshold cellularity of >600 cells/mm^2 (correlation of FGF-R and cell density $r = 0.77$; $p < 0.001$). TEM analysis revealed cell-rich intimal areas comprised of foam cells and SMCs with numerous cytoplasmic organelles. Signaling partial SMC dedifferentiation, the morphometric volume fraction of organelles/cytoplasm was 0.46 ± 0.15 (n = 21). This ratio correlated significantly with intimal cellularity ($r = 0.67$; $p < 0.001$), but not with FGF-R. In 8 lesions, macrophage clusters (CD68$^+$ cells) were seen that spanned central necrotic regions and luminal plaque margins, indicating sites of plaque rupture. TUNEL$^+$ cells (23 ± 17%) were predominantly found in these regions, while TEM revealed SMCs and macrophages exhibiting typical TEM features of apoptosis (nuclear alterations, cell condensation, loss of adhesion, membrane budding, apoptotic bodies). Most interestingly, this density of apoptotic cells correlated inversely with cellularity ($r = 0.39$; $p < 0.05$).

Conclusion: Our data demonstrate FGF-R expression in the cell-rich fibrous cap, but not in central or macrophage-rich areas. The interrelationship of FGF-R with cell density, SMC dedifferentiation and apoptosis indicates FGF-R to be a pathogenic factor in human plaque formation, and in addition, suggests that FGF-R contributes in counterbalancing apoptotic events.

1078-49 The Role of Vascular Components in Carotid Plaque Hemorrhage, an Immunocytochemical Approach

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Background: A complete immunohistochemical characterization of the plaque accident in carotid arteries is still lacking. Because of this, the components of 174 surgically excised carotid endarterectomies were examined to get knowledge about their role in the genesis of intraplaque hemorrhage without rupture of the cap (IPH).

Methods: The specimens were serially sliced, aside from classical histological stainings, immunophenotyping of cells was performed with monoclonal antibodies in single and double stainings.

Results: In 38 IPH, serial sections presented clean intimal surfaces and dense collagen caps. No thrombi were observed and a continuos, non-damaged row of endothelial cells CD31+ and CD34+ were found. Plaques presented extensive hemorrhages and were highly vascularized, with neoformed vessels CD34+ and CD31+. Macrophages (CD68+) and T-lymphocytes (CD45RO+) were found to be in close contact to neoformed vessels, and the latter in some cases, migrating through the endothelial cells. The base of the IPH showed in 24/38 (63%) cases, neoformed vessels surrounded by mild to extensive mononuclear infiltrates and in 5/38 (13%) histological signs of old hemorrhages surrounding those vessels could be observed. In the remaining 136 (no-IPH) cases, only avascular or mild vascularized plaques were found ($p < 0.0001$).

Conclusion: IPH are not related to cap erosion, but to plaque vascularization. Lipid cores were highly vascularized with neoformed vessels with macrophages and T-cells in close contact and in some cases disrupting the endothelium. The abrupt growing of the lipid cores and/or an overproduction of metalloproteins, and/or oxygen free radicals by the macrophages could lead to the breakdown of core vessels and the generation of IPH without any connection with the lumen.

1078-50 Soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) and Intercellular Adhesion Molecule-1 (sICAM-1) Correlates With Carotid Thickness

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Background: Intima-to-medial thickness (IMT) of carotid arteries is an index of atherosclerosis and has been associated with traditional risk factors. Expression of adhesion molecules has also been implicated in atherogenesis.

Methods: We studied 92 outpatients (48 males, 65 ± 9 years) to evaluate the association of sVCAM-1, sICAM-1 and interleukin-6 (IL-6) with carotid thickness. All subjects underwent a two-dimensional ultrasound of both carotids. IMT was measured on the far wall on the distal common carotid and bifurcation. Serum markers were measured by ELISA.

Results: sVCAM-1 and sICAM-1 were significantly correlated with IMT of the common carotid ($r = 0.32$ and $r = 0.31$; respectively, $p < 0.01$) and carotid bifurcation ($r = 0.3$ and $r = 0.24$; respectively, $p < 0.01$). The table presents sVCAM-1 and sICAM-1 levels according to tertiles of common carotid IMT:

	High tertile	Intermediate	Low tertile	p
sVCAM-1	773 ± 419	649 ± 260	563 ± 191	<0.05
sICAM-1	376 ± 171	275 ± 111	263 ± 112	<0.05

There was no association between IL-6 and carotid IMT. After adjustment for traditional risk factors (age, hypertension, diabetes, smoking and hypercholesterolemia), sVCAM-1 levels remained significantly associated with commom carotid and carotid bifurcation IMT, while sICAM-1 levels correlated only with common carotid IMT.

Conclusions: Adhesion molecules are associated with carotid IMT, an index of early atherosclerosis. These data further support a link between inflammation and arterial pathology in humans.

1078-51 Brief Myocardial Ischemia Attenuates Platelet Aggregation in Remote, Damaged and Stenotic Rabbit Carotid Arteries

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Background: Recent studies from our laboratory revealed that platelet-mediated thrombosis in damaged and stenotic canine coronary arteries is significantly attenuated when injury + stenosis is preceded by brief occlusion of the culprit vessel. We further identified adenosine, released from the ischemic/reperfused myocardium, as a crucial mediator of this antiplatelet