MRI Atherosclerotic Plaque Characterization

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Vulnerable Plaque

Different Types of Vulnerable Plaque

A. Normal
B. Rupture-Prone Vulnerable Plaque
C. Ruptured / Healing Vulnerable Plaque
D. Erosion-Prone Vulnerable Plaque
E. Eroded Vulnerable Plaque
F. Vulnerable Plaque with Intra-Plaque Hemorrhage
G. Vulnerable Plaque with Calcified Nodule
H. Critically Stenotic Vulnerable Plaque

Naghavi et al, Circulation 2003
Need For Imaging

• Detect asymptomatic patients
  • High risk for future cardiovascular events
  • High risk for progression
  • Benefit from preventive or therapeutic interventions

• Non-invasive
  • Risk prediction
  • Follow up

• Provide information of
  • Vessel lumen and wall size
  • Tissue composition
  • Status of inflammation
Imaging Goals I: Morphology

Lumen – Wall – Area – Volume
Wall thickness – Mean – Max/Min – IMT

Angiography Underestimates Plaque Burden
Imaging Goals II: Lumen Surface Characteristics

Intact, thick fibrous cap

Ruptured cap with intraplaque hemorrhage
Imaging Goals III: Tissue Composition

- Extracellular Matrix
- Intraplaque Hemorrhage
- Mural Thrombus
- Lipid Rich Necrotic Core
- Calcification
- Plaque neovasculature

Coronary

Carotid
Carotid Artery Atherosclerosis

- Stroke/TIA
- Location
- Carotid endarterectomy (CEA)
  - Access to plaque specimen
    - In vivo and Ex vivo studies
    - Histology
MRI Carotid Techniques: Multi-Contrast Protocol

- Bright/Black Blood
- MDIR/QIR sequences
- Contrast agent application
- Quantitative information
  - Lumen narrowing
  - Plaque burden
  - Tissue composition

MRI Based Lesion Type for the Carotid

MRI Study of the Advanced Carotid Lesion

Hemorrhage - Recent (Type VI)

Mallory’s Trichrome

## MRI Accuracy

<table>
<thead>
<tr>
<th></th>
<th>Lipid-Rich Necrotic Core(^1)</th>
<th>Fibrous Cap (thick vs. thin or ruptured)(^2,3)</th>
<th>Intraplaque Hemorrhage(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>85%</td>
<td>81%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>92%</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td><strong>Kappa</strong></td>
<td>0.69</td>
<td>0.83</td>
<td>0.82</td>
</tr>
</tbody>
</table>

1. Yuan, et al., *Circulation* 2001; 104:2051-6
Quantitative Evaluation of Plaque Composition by in vivo MRI

Plaque Composition by MRI
[as percentage of the wall]

Plaque Composition by Histology
[as percentage of the wall]

Lipid/Necrotic Core MRI vs. Histology: p=.1
Loose Fibrous Matrix MRI vs. Histology: p=.1
Calcium MRI vs. Histology: p<.0001
(Dense) Fibrous Tissue MRI vs. Histology: p=.4

Contrast Enhanced MRI

PRE:

POST:

T1W Imaging – Black Blood

Yuan et al., JMRI 2002; 15:62-7
Wasserman et al, Radiology, 2002
CE-MRI Protocol

MRI Protocol

- MRI: 2DSPGR (TR / TE = 100 / 3.5 msec)
- Contrast agent: 20 ml Omniscan (Gadolinium-based) administered at 2ml/sec
Staining
- HAM56 for macrophages (red)
- Ulex for endothelial cells (black/brown)

Quantification
- Regions containing neovasculature / macrophages photographed at high power
- Measured HAM56 positive area
- Identified neovessel boundaries and measured area
- Normalized by total plaque area
DCE-MRI and Neovasculature

Fractional Vascular Area (%) vs. $v_p$ (%) graph

$r = 0.76$
$p = 0.0003$

Correlation Between $K^{\text{trans}}$ (MRI) and Fractional Macrophage Area (Histology)

$R = 0.74 \quad p < 0.001$

Elevated $K^{\text{trans}}$ associated with:

- Macrophage content
- Smoking
- Lower HDL

Kerwin et al, *Radiology, in press*
Serial Human Carotid Imaging - MRI

Fibrous cap rupture – 10 month follow up

Comparison of Patients from China and US with Recent TIA or stroke

- Larger lipid cores in Chinese group (12.0 vs. 7.1 mm²; p = 0.01)
- More calcification in US group (4.2 vs. 1.1 mm²)
- Lipid-lowering drugs in only 26% vs 63% in Chinese group

Saam T, et al. ATVB, 2005
Right CCA From a 59-year-old Chinese Patient

**Imaging**

**Presence of Intraplaque Hemorrhage Stimulates Progression of Carotid Atherosclerotic Plaques**

A High-Resolution Magnetic Resonance Imaging Study

Norihide Takaya, MD, PhD; Chun Yuan, PhD; Baocheng Chu, MD, PhD; Tobias Saam, MD; Nayak L. Polissar, PhD; Gail P. Jarvik, MD, PhD; Carol Isaac, RVT; Judith McDonough, BS; Cynthia Natiello, RN; Randy Small, HT; Marina S. Ferguson, MT; Thomas S. Hatsuuki, MD

**Background**—Previous studies suggest that erythrocyte membranes from intraplaque hemorrhage into the necrotic core are a source of free cholesterol and may become a driving force in the progression of atherosclerosis. We have shown that MRI can accurately identify carotid intraplaque hemorrhage and precisely measure plaque volume. We tested the hypothesis that hemorrhage into carotid atheroma stimulates plaque progression.

**Methods and Results**—Twenty-nine subjects (14 cases with intraplaque hemorrhage and 15 controls with comparably sized plaques without intraplaque hemorrhage at baseline) underwent serial carotid MRI examination with a multicontrast weighted protocol (T1, T2, proton density, and 3D time of flight) over a period of 18 months. The volumes of wall, lumen, lipid-rich necrotic core, calcification, and intraplaque hemorrhage were measured with a custom-designed image analysis tool. The percent change in wall volume (6.8% versus −0.15%; *P*=0.009) and lipid-rich necrotic core volume (28.4% versus −5.2%; *P*=0.001) was significantly higher in the hemorrhage group than in controls over the course of the study. Furthermore, those with intraplaque hemorrhage at baseline were much more likely to have new plaque hemorrhages at 18 months compared with controls (43% versus 0%; *P*=0.006).

**Conclusions**—Hemorrhage into the carotid atherosclerotic plaque accelerated plaque progression in an 18-month period. Repeated bleeding into the plaque may produce a stimulus for the progression of atherosclerosis by increasing lipid core and plaque volume and creating new destabilizing factors. (*Circulation. 2005;111:2768-2775.*)
Methods

- Twenty-nine patients participating in a long term MRI progression study were divided into two groups:
  - 14 patients who had carotid plaques with intraplaque hemorrhage
  - 15 patients who had comparable plaques without intraplaque hemorrhage at the baseline MRI examination
- The volume of wall, lumen, lipid-rich necrotic core, and hemorrhage were measured at baseline and after 18 months
Intraplaque Hemorrhage and Plaque Progression

Takaya et al, *Circulation* 2005; 111:2768
## Intraplaque Hemorrhage and Plaque Progression

<table>
<thead>
<tr>
<th></th>
<th>IPH</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=14)</td>
<td>(n=15)</td>
<td></td>
</tr>
<tr>
<td>Lumen Volume</td>
<td>-8.5 ± 12.2</td>
<td>1.5 ± 7.9</td>
<td>0.014</td>
</tr>
<tr>
<td>Wall Volume</td>
<td>6.8 ± 7.9</td>
<td>-0.15 ± 5.1</td>
<td>0.009</td>
</tr>
<tr>
<td>LR/NC Volume</td>
<td>28.4 ± 29.7</td>
<td>-5.2 ± 17.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Takaya et al, *Circulation* 2005; 111:2768
• One-click detection of lumen / wall boundaries
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CASCADE

- One-click detection of lumen / wall boundaries
- Automated multi-contrast image registration
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• Automated multi-contrast image registration
CASCADE

- One-click detection of lumen / wall boundaries
- Automated multi-contrast image registration
- Morphology Enhanced Probabilistic Plaque Segmentation (MEPPS)

Coronary Imaging

3D spiral

RCA wall

1mm

RCA wall

RV

Healthy subjects

Fibrin binding Gd-labeled Contrast Agent

Botnar, Buecker, Wiethoff et al. Circulation 2004

EP-2104R (EPIX Medical Inc.)
Thrombus - Fibrin-targeted MR CA

Pre-Injection

CCA right uninjured

CCA left injured

Thrombus CCA left

Post-Injection 30 min.

Fibrin specific
Cyclic peptide (EPIX)

Anti-angiogenic Effects of Fumagillin Nanoparticles in Atherosclerotic Rabbits

Treatment 1 Wk Post

$\alpha_\nu\beta_3$-Targeted With Drug
(30µg Fumagillin/kg)

$\alpha_\nu\beta_3$-Targeted Without Drug

Winter et al.
MR Atherosclerosis Imaging

• Current status
  • Soft tissue contrast
  • Safe
  • Depicts vessel wall/burden
  • Tissue characterization
  • Serial studies

• Future
  • Atherosclerosis progression
  • High resolution coronary imaging
  • Relationship of systemic atherosclerosis
  • Targeted contrast enhancement