Clinical and Histological Significance of Gadolinium Enhancement in Carotid Atherosclerotic Plaque

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Background and Purpose—Although the ability of MRI to investigate carotid plaque composition is well established, the mechanism and the significance of plaque gadolinium (Gd) enhancement remain unknown. We evaluated clinical and histological significance of Gd enhancement of carotid plaque in patients undergoing endarterectomy for carotid stenosis.

Methods—Sixty-nine patients scheduled for a carotid endarterectomy prospectively underwent a 3-T MRI. Carotid plaque enhancement was assessed on T1-weighted images performed before and 5 minutes after Gd injection. Enhancement was recorded according to its localization. Histological analysis was performed of the entire plaque and of the area with matched contrast enhancement on MR images.

Results—Gd enhancement was observed in 59% patients. Three types of carotid plaques were identified depending on enhancement location (shoulder region, shoulder and fibrous cap, and central in the plaque). Fibrous cap rupture, intraplaque hemorrhage, and plaque Gd enhancement was significantly more frequent in symptomatic than in asymptomatic patients ($P=0.043$, $P<0.0001$, and $P=0.034$, respectively). After histological analysis, Gd enhancement was significantly associated with vulnerable plaque (American Heart Association VI, $P=0.006$), neovascularization ($P<0.0001$), macrophages ($P=0.030$), and loose fibrosis ($P<0.0001$). Prevalence of neovessels, macrophages, and loose fibrosis in the area of Gd enhancement was 97%, 87%, and 80%, respectively, and was different depending on the enhancement location in the plaque. Fibrous cap status and composition were different depending on the type of plaque.

Conclusions—Gd enhancement of carotid plaque is associated with vulnerable plaque phenotypes and related to an inflammatory process. (Stroke. 2012;43:00-00.)

Key Words: carotid plaque • gadolinium enhancement • high-resolution MRI • plaque vulnerability • stroke

Early detection of vulnerable carotid plaque is paramount to improving stroke prevention. High-resolution MRI is a useful noninvasive tool for characterizing atherosclerotic plaque composition and provides excellent images of the arterial wall. Plaque rupture, a thin fibrous cap with large lipid rich-necrotic core, ulceration, thrombus, and intraplaque hemorrhage identified on high-resolution MRI are associated with a higher risk of stroke, even when stenosis is moderate.1–7

Gadolinium chelates are contrast agents routinely administered for contrast-enhanced MR angiography. Postcontrast black blood images also improve the characterization of carotid plaques based on their enhancement properties. Gadolinium enhancement can be visualized in the fibrous cap, in the adventitia, or in the plaque itself. The mechanisms underlying gadolinium enhancement of carotid plaques are complex. Gadolinium-based contrast agents are known to distribute to the extracellular extravascular space. Thus, the enhancement may be due to increased wash-in of gadolinium-based contrast agent (increased perfusion and permeability), increased distribution volume (increased extracellular volume), and/or decreased washout.8 The enhancement in carotid plaques is indistinctly attributed to pathophysiological processes such as neovascularization or inflammation and to vessel wall composition and organization. A number of studies have evaluated carotid plaque characterization with high-resolution MRI but only few studies, performed on a small number of patients, have focused on gadolinium enhancement in carotid arteries.9–14 Clinical significance and
physiopathological mechanisms of gadolinium enhancement in carotid arteries remain largely unexplored.

Accordingly, the present study assessed the clinical and histological significance of gadolinium enhancement of carotid plaque using 3-T high-resolution MRI in a large cohort of subjects undergoing carotid endarterectomy for carotid stenosis. First, the evaluation of gadolinium enhancement and its relation to clinical symptoms, MRI, and histological data were performed. Then, histological analysis of area corresponding to localization of gadolinium enhancement was performed.

**Materials and Methods**

**Study Population**

Between September 2008 and March 2011, 69 patients scheduled for carotid endarterectomy for symptomatic or asymptomatic carotid stenosis at the University Hospital of Lyon were recruited for the study after obtaining informed consent and after exclusion of contraindications of MRI and gadolinium injection. The Institutional Review Board approved the consent form and study protocols. Patients underwent MRI of their carotid artery within 30 days of the surgical procedure to reduce potentials errors in correlating imaging with histopathology. Stroke was assessed by clinical examination by a referring a vascular surgeon and a stroke neurologist. Patients with a recent stroke related to a cardiac source, including atrial fibrillation, intracardiac thrombus, or patent foramen ovale, were excluded from this study. Patients were considered symptomatic when an ipsilateral carotid-related neurological event was reported in the last 6 months.

**MRI Protocol**

Imaging was performed on a 3-T MR system (Achieva scanner; Philips Healthcare, Best, The Netherlands) with a dual surface coil (Sense Flex S; Philips Healthcare). After a survey to determine the position of the carotid bifurcation, time-of-flight, T1-, and proton density-weighted sequences were acquired centered on the identified carotid plaque perpendicular to the main carotid axis. Contrast-enhanced (CE) MR angiographic coronal images were obtained from this study. Gadolinium CE was characterized as 0 (absent) and 1 (present). Thrombus was not recorded. We categorized variables as 0 (absent) and 1 (present). Thrombus was not recorded. We included juxtaluminal hemorrhage in IPH and we recorded the FC status regardless of the presence or not of IPH. Criteria used are summarized in online-only Data Supplement Methods III.

**Image Review**

Before quantitative analysis, all images were reviewed by an experienced observer to assess image quality. Image quality was rated on a 5-point scale dependent on the overall signal-to-noise ratio. Images with a score <3 were excluded from the analysis. Two independent readers blinded to clinical and histological data analyzed MR images. Cases of disagreement between readers were solved by consensus. The degree of carotid artery stenosis was assessed on MR angiography according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Plaque thickness was assessed on the postinjection T1-weighted images. Presence of intraplaque hemorrhage (IPH), fibrous cap (FC) rupture, and a large lipid core (>50% of the vessel wall thickness) were rated as 0 (absent) and 1 (present). Thrombus was not recorded. We included juxtaluminal hemorrhage in IPH and we recorded the FC status regardless of the presence or not of IPH. Criteria used are summarized in online-only Data Supplemental Methods II.

Both observers visually analyzed signal changes in the vessel wall in the postcontrast images compared with corresponding precontrast images and contoured the region of interest where they found uptake. Using in-house software for manual image registration, the mean signal intensity (SI) for each region of interest was measured and normalized to the SI in the adjacent sternoclavimastoid muscle. The percentage of SI change was automatically calculated as follows: (SI plaque post×SI muscle pre)/(SI plaque pre×SI muscle post). Precautions were taken to exclude images with prominent flow artifacts. When pre- and postcontrast images could not be coregistered, data were excluded from the analysis. Gadolinium CE was characterized by its localization in the plaque: FC, shoulder region, or central to the plaque. Adventitial enhancement was not investigated, because the adventitia is not included in histological specimens.

**Histological Processing**

Carotid endarterectomy was performed within 1 month after MRI according to a technique described by Chevalier,16 which preserves the entire plaque of the internal carotid. Immediately after carotid endarterectomy, the excised plaque was marked with a blue ink line along the internal carotid, fixed in formalin, and embedded in paraffin. No decalcification was performed. Transverse sections were performed throughout the length of endarterectomy specimen at intervals of 2 mm. Six to 8 adjacent 5-μm transverse sections were taken from each wax block. Each section was stained with hematoxylin and eosin, Picosiris red for collagen, mouse antihuman monoclonal antibody CD68 (macrophage), and CD34 (endothelial cells). A researcher experienced in vascular pathology and blind to the imaging results examined all of the histology sections of each specimen. The following features were graded on a simple semiquantitative scale previously published by Lovett et al17: surface thrombus, thick, thin (<200 μm) or ruptured FC, IPH, neovascularization, and macrophage infiltration. Loose fibrosis was defined as fibrous tissue rich in nonfibrillar extracellular matrix with thin and noncondensed collagen fibers and was graded: <30% of total fibrous tissue or >30% of total fibrous tissue. Plaques were classified according to the American Heart Association classification of coronary atherosclerosis and according to the Lovett and Redgrave classification.17,18

**Correlation Between MRI and Histology**

Histology sections were matched to MR images based on the blue line, the relative distance from the carotid bifurcation, the gross morphological features, and the presence or absence of large regions of dense calcification, which can be readily identified by MRI and histology (online-only Data Supplement Methods III). One experienced radiologist and one experienced vascular pathologist performed the coregistration. Histological analysis was performed on the enhancement area, focusing on the presence or the absence of neovessel, macrophage, and loose fibrosis and the FC status and its composition.

**Statistical Analysis**

Statistical analysis was performed with SPSS Version 15.0 (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean and SD or range. Categorical variables were expressed as frequency and percentages. χ2 or a Fisher exact test was performed to compare categorical variables. The Mann–Whitney U test was used to compare continuous variables with categorized variables. Probability values <0.05 were considered statistically significant.

**Results**

Of the 69 patients enrolled, 6 patients were excluded because of issues related to MRI (quality score <3 in 5 cases and improper matching between pre- and postgadolinium T1 images in one case) and 4 because of issues related to histology (specimen damaged during histological processing because of massive calcification). A total of 59 patients were analyzed. Demographic characteristics and MRI results are summarized in online-only Data Supplemental Results IV. Mean delay between MRI and endarterectomy was 10.8 days (range, 1–30 days). Nineteen patients were symptomatic (14...
strokes, 4 transient ischemic attacks, and one amaurosis) with mean delay between neurological event and MRI of 41 days (range, 1–158 days).

**CE-MRI Results**
Mean plaque thickness and mean NASCET degree of stenosis assessed on MRI were 4.5 mm (range, 2.8–6.9 mm) and 70% (range, 30%–90%) without a difference according to the symptom ($P=0.288$ and $P=0.138$, respectively). FC rupture and IPH were significantly more frequent in symptomatic than in asymptomatic patients (42% versus 18%, $P=0.043$; 53% versus 10%, $P<0.0001$, respectively).

Plaque contrast enhancement (CE+) was observed in 35 of 59 patients (59%) with a statistical difference ($P=0.034$) between symptomatic (n=15 [79%]) and asymptomatic patients (n=20 [50%]). Plaque CE was observed in an average of 2.3 images (range, 1–5) for each CE+ patient with a mean enhancement ratio of 1.43 ($\pm 0.17$; range, 1.20–1.89). Enhancement of the FC was never observed alone and has always been associated with a shoulder enhancement. Central and shoulder enhancements were never observed together. Carotid plaques were then classified in 3 types: (1) Type 1: shoulder region enhancement (n=4 [11%]); (2) Type 2: association of shoulder and fibrous cap enhancement (n=8 [23%]); and (3) Type 3: central plaque enhancement (n=23 [66%]).

No statistical association was observed between plaque types and symptom ($P=0.109$).

**Pathological Results**
Sensitivity and specificity of high-resolution MRI in the detection of IPH, FC rupture, and large lipid core were, respectively, 72% and 98%, 69% and 85%, and 68% and 75%. Histological results are summarized in Table 1. Vulnerable plaques (American Heart Association VI or Lovett Grade 3–4) were significantly associated with CE+ plaques ($P=0.006$ and $P<0.0001$, respectively) as well as thin or ruptured FC ($P=0.037$), neovascularization ($P<0.0001$), macrophages ($P=0.030$), and loose fibrosis ($P=0.0001$). There was no statistically significant differences between CE+ and CE− plaques for surface thrombus ($P=0.700$), a large lipid core ($P=0.243$), or IPH ($P=0.056$).

**Correlation Between CE-MRI and Histology**
For analysis of enhancement localization, good coregistration between MR images and histological slices was obtained in 30 patients. Prevalence of neovessels, macrophages, and loose fibrosis in the area of gadolinium enhancement was 97%, 87%, and 80% and was different depending on the enhancement location in the shoulder region, in the FC, or central in the plaque (Table 2). FC status and composition were different depending on the type of plaque (online-only Data Supplement Results V). FC rupture was observed in 4 cases (22%) of Type 3 plaques, whereas FC was intact in all cases of Type 1 or Type 2 plaques ($P=0.307$). Prevalence of loose fibrosis in the cap was significantly different between plaque types: 25%, 100% and 50% in Type 1, 2, and 3 plaques, respectively ($P=0.009$).

### Table 1. Results of the Histological Examination of Carotid Plaques and Comparison Between Patients With Contrast Enhancement in the Plaque on MRI (CE+) and Patients Without (CE−)

<table>
<thead>
<tr>
<th>Features, No. (%)</th>
<th>Patients (n=59)</th>
<th>CE+ Plaques (n=35)</th>
<th>CE− Plaques (n=24)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA Type VI plaques</td>
<td>25 (42)</td>
<td>20 (57)</td>
<td>5 (21)</td>
<td>0.006</td>
</tr>
<tr>
<td>Lovett classification*</td>
<td>Grade 2</td>
<td>20 (34)</td>
<td>4 (11)</td>
<td>16 (67)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>27 (46)</td>
<td>19 (54)</td>
<td>8 (33)</td>
<td>0.307</td>
</tr>
<tr>
<td>Grade 4</td>
<td>12 (20)</td>
<td>12 (34)</td>
<td>0</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Surface thrombus</td>
<td>6 (10)</td>
<td>4 (11)</td>
<td>2 (8)</td>
<td>0.700</td>
</tr>
<tr>
<td>Large lipid core &gt;50%</td>
<td>30 (51)</td>
<td>20 (57)</td>
<td>10 (42)</td>
<td>0.243</td>
</tr>
<tr>
<td>IPH</td>
<td>18 (30)</td>
<td>14 (40)</td>
<td>4 (17)</td>
<td>0.056</td>
</tr>
<tr>
<td>Thin or ruptured FC</td>
<td>19 (32)</td>
<td>15 (43)</td>
<td>4 (17)</td>
<td>0.037</td>
</tr>
<tr>
<td>Neovascularization</td>
<td>36 (61)</td>
<td>28 (80)</td>
<td>8 (33)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Macrophages</td>
<td>39 (66)</td>
<td>27 (77)</td>
<td>12 (50)</td>
<td>0.030</td>
</tr>
<tr>
<td>Loose fibrosis</td>
<td>33 (56)</td>
<td>27 (77)</td>
<td>6 (25)</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

CE indicates contrast-enhanced; AHA, American Heart Association; IPH, intraplaque hemorrhage; FC, fibrous cap.

*Lovett classification is a semiquantitative grading scale based on the presence of histological features.17 Grade 2 corresponds to a probably stable plaque, Grade 3 to a probably unstable plaque and Grade 4 to a definitely unstable plaque.

Type 1 plaques showed a high incidence of neovessels and macrophages in the shoulder region with an intact and dense FC without neovessel (Figure 1). Type 2 showed neovessels and macrophages in the shoulder region with a FC mainly composed by loose matrix with very few neovessels (Figure 2). Type 3 showed cap rupture in 4 cases with inflammatory reaction (Figure 3) or neovessels within a large area of loose matrix (Figure 4).

**Discussion**
Carotid plaque gadolinium enhancement in patients with carotid stenosis is associated with symptomatic and vulnerable plaques defined by histology. Our findings further show that histological composition of enhancement area varies depending on the location highlighting different mechanisms of gadolinium uptake. In addition, carotid plaque gadolinium enhancement allows definition of different types of plaques likely corresponding to different stages of plaque vulnerability.

Gadolinium usually used for the assessment of the stenosis on MR angiography can be also used to improve carotid plaque characterization more specifically to evaluate FC.
integrity and lipid core delineation.19,20 This is one of the first studies to confirm that gadolinium enhancement is more frequent in symptomatic plaque and associated with vulnerable plaques according to standard histological classifications (American Heart Association, Lovett).17,18 The spatial association of CE with neovascularization and inflammation supports these results. Inflammation and neovascularization are both well known as hallmarks of vulnerable plaque.21 Focal enhancement is most often localized in the shoulder region. Histological correlation finds neovessels in all cases. Several authors have already established the strong correlation between gadolinium enhancement and neovascularization in human carotid plaques.9–11 Plaque gadolinium uptake is explained by the endothelial dysfunction of these intraplaque microvessels,22 which result in vascular leakage and perivascular accumulation of gadolinium. The preferential localization of enhancement in the shoulder region is in agreement with histopathology, which demonstrated that most microvessels were located in the shoulder region of the atherosclerotic plaque.23 Comparison between isolated shoulder region enhancement and associated shoulder+FC enhancement revealed differences in FC composition. Cai19 has already described that FC predominantly composed of organized and dense collagen demonstrated moderate enhancement, whereas FC with loose matrix, neovasculature, and inflammatory cell infiltrates were associated with stronger enhancement.

In our study, FC enhancement was always associated with shoulder enhancement. Prevalence of loose fibrosis in enhanced FC was 100%, whereas prevalence of neovascularization was only 12.5%. This suggests that FC enhancement could be related to gadolinium diffusion from microvessels localized in the shoulder region to the FC. Loose fibrosis, observed in FC, is probably related to a degradation of the extracellular matrix by the matrix metalloproteinase leading to increase tissue fragility and enhance the risk of FC rupture.24 Therefore, FC enhancement can be interpreted as a prerupture sign. The combination of shoulder and FC enhancement could correspond to a more advanced lesion versus isolated shoulder enhancement with a higher risk of FC rupture.

Central enhancement corresponds to plaque with a large loose fibrosis area or FC rupture. Correlation between enhancement and extravascular extracellular space has already been established by Kerwin.11,12 Cai also reported strong CE of the loose matrix.19 This is explained by gadolinium diffusion from the arterial lumen (of the carotid artery or of the neovessels) into the extravascular extracellular space. We confirmed that loose fibrosis was observed in the enhanced area in 80% cases. Our finding confirms the role of the loose fibrosis in the higher diffusion rate of the gadolinium contrast agent. The gadolinium could come either from the lumen of the internal carotid artery and diffuse into the plaque through a “leaky” FC rich in loose fibrosis or from the lumen of neovessels very often associated with the loose fibrosis.

A large area of loose fibrosis in the plaque may result from advanced extracellular matrix degradation and may reveal unstable and prone to rupture plaque. In contrast, others have
shown that loose matrix is produced in plaque healing of coronary arteries in patients with silent plaque rupture and that the larger amount of loose matrix formation in the symptomatic artery may occur in response to previous FC ruptures in this artery. Studies focused on CE in carotid plaque rarely report FC rupture as a cause of plaque enhancement. CE is easily explained by gadolinium entrapment in the plaque, but it is likely to be multifactorial. In our study, we observed neovascularization close to the FC rupture (in 2 of 4 cases). Reproducibility of FC status assessment has been shown to be moderate using noncontrast MRI. Kwee et al. has demonstrated that FC visualization can be improved with CE-MRI. In our experience, FC rupture is not always easy to affirm in MRI, particularly when the FC is not viewed on T1 postcontrast. The assessment of the narrow band between lumen and arterial wall on time-of-flight sequences is often challenging, particularly in calcified plaques. In our study, in 3 cases of diffuse enhancement in which FC rupture was present on histology, FC rupture was not detected on the MR images. Enhancement analysis may be helpful to better characterize the FC status.

**Conclusion**

Carotid plaque gadolinium enhancement identified on MRI seems to be a marker of carotid plaque vulnerability. Neovascularization, inflammation, and loose matrix, known to be histological features of vulnerable atherosclerotic plaques, are well matched with localization of plaque enhancement. The analysis of this parameter provides complementary information on the carotid plaque status. Carotid plaque enhancement could be assessed along with FC integrity, size of the lipidic core, or presence of IPH in future prospective trial to improve carotid plaque characterization.

**Disclosures**

None.

**References**


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SUPPLEMENTAL MATERIAL

S1. Supplemental Methods: MRI protocol and imaging parameters

The dual surface coil (Sense Flex S, Philips Healthcare) was positioned on top of the mandibular angles. This coil included two elements for bilateral carotid artery imaging and was combined with a head holder to prevent head rotation and stabilize position.

After a survey to determine the position of the carotid bifurcation (axial and parasagittal balanced steady state free precession sequence bTFE), Time-of-Flight (TOF), T1 and proton density (PD) weighted sequences described below were acquired centered on the identified carotid plaque perpendicular to the main carotid axis.

- A 3D TOF multiple overlapping thin slab acquisition MR angiography (MRA) sequence was performed using a spoiled gradient echo (T1-FFE) sequence with the following parameters: repetition time/echo time, 25.0/3.44 ms; flip angle: 10°; slice thickness: 1.6 mm (interpolated to 0.8 mm); in plane resolution 0.45 mm x 0.45 mm interpolated to 0.25 mm x 0.25 mm, number of averages = 3.

- Six transverse slices of ECG triggered T1-weighted images were acquired with a turbo spin echo (TSE) sequence using a double inversion recovery (DIR) black-blood preparation pulse and spectrally-selective inversion recovery fat saturation (SPIR) pulse. The imaging parameters included: repetition time/echo time, 1 heart beat/23 ms; flip angle: 90°; slice thickness: 2 mm (gap of 1 mm); in plane resolution 0.45 mm x 0.45 mm interpolated to 0.25 mm x 0.25 mm, number of averages = 4, parallel imaging (SENSE) acceleration factor: 2 (in the RL direction); TSE factor = 9.

- The PD-weighted TSE sequence was similar to the T1-weighted sequence, with the following modifications: Repetition time/echo time = 2 heart beats/33 ms, number of averages = 2.

- Contrast-enhanced MRA (CE-MRA) coronal images were obtained with a 3D T1-FFE Contrast-enhanced timing-robust angiography (CENTRA) imaging technique before and during an injection of 30 ml of a Gadolinium-based contrast agent (DOTAREM®, Guerbet, France), followed by a 10 ml saline flush, delivered at 2 ml/s with the following parameters: repetition time/echo time: 4.5/1.7 ms; 150 slices of 1 mm interpolated to 0.5 mm, in-plane resolution: 0.63 mm x 0.63 mm interpolated to 0.5 mm x 0.5 mm; parallel imaging (SENSE) acceleration factor: 2 (in the RL direction); time to center of k-space: 2.5 s.

- Six T1-weighted black-blood TSE transverse slices were repeated 5 minutes after the gadolinium injection, at the same level and with the T1w pre-injection sequence. The total acquisition time was approximately 45 minutes.
S2. Supplemental Methods: MRI criteria for carotid plaques features identification.1-4

Lipid rich-Necrotic core (LR-NC): iso-signal on TOF and T1-weighted images and hyposignal to iso-signal on PD-weighted images.  
Large LR-NC > 50%: Measurement was performed on the image showing the thicker LR-NC by dividing the thickness of the LR-NC in the radial direction by the thickness of the plaque on this slice.  
Fibrosis: iso-signal on TOF, hyper signal on PDw, iso or hyposignal on T1w, hypersignal on T1w post gadolinium.  
Calcification: asignal on TOF, T1, PD and T1 post gadolinium weighted images.  
Fibrous cap rupture: Disrupted dark band or no visible dark band adjacent to the lumen on TOF angiograms and/or presence of FC discontinuity on post contrast injection T1-weighted images.  
IntraPlaque Hemorrhage: Hyperintense signal on TOF and T1w images and/or Hyperintense signal on precontrast mask of CE-MRA.

S3. Supplementals Methods: Methods used for spatial correlation between MR images and histological slices.

This figure illustrates spatial correlation between endarterectomy specimen cross sections and MR images. (A): Entire specimen marked with a blue line and transverse sections throughout the length of the specimen (interval 2 mm). (B) and (C): Corresponding 6 transverse MR slices of the T1 weighted sequences, pre (B) and post (C) gadolinium injection respectively. (D): first 5-µm transverse sections of each corresponding block, as well as 5 transverse section corresponding to the enhancement (arrows).
**S4. Supplementals Results:** Demographic and MRI characteristics of the population.

<table>
<thead>
<tr>
<th>Cardiovascular risk factor</th>
<th>Symptomatic (n=19)</th>
<th>Asymptomatic (n=40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>71 (54-87)</td>
<td>70 (41-85)</td>
<td>0.716</td>
</tr>
<tr>
<td>Male gender</td>
<td>14 (74)</td>
<td>35 (87)</td>
<td>0.186</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (58)</td>
<td>25 (62)</td>
<td>0.735</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (21)</td>
<td>17 (42)</td>
<td>0.108</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (84)</td>
<td>33 (82)</td>
<td>0.870</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7 (37)</td>
<td>13 (32)</td>
<td>0.742</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>3 (16)</td>
<td>14 (35)</td>
<td>0.128</td>
</tr>
<tr>
<td>PAD</td>
<td>2 (10)</td>
<td>11 (27)</td>
<td>0.142</td>
</tr>
<tr>
<td><strong>Biological results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL chol mmol/l</td>
<td>2.4 (1.3-4.5)</td>
<td>2.2 (0.7-4.3)</td>
<td>0.223</td>
</tr>
<tr>
<td>Hs CRP mg/l</td>
<td>5.8(0.5-30.5)</td>
<td>3.6 (0.2-15.0)</td>
<td>0.129</td>
</tr>
<tr>
<td>GFR ml/min</td>
<td>86.5 (51-151)</td>
<td>80.8 (23-142)</td>
<td>0.280</td>
</tr>
<tr>
<td><strong>Use of drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>17 (90)</td>
<td>33 (83)</td>
<td>0.486</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>8 (42)</td>
<td>26 (65)</td>
<td>0.141</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>19 (100)</td>
<td>39 (98)</td>
<td>0.107</td>
</tr>
<tr>
<td><strong>MRI Findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NASCET %</td>
<td>67.6 (40-90)</td>
<td>72.9 (50-90)</td>
<td>0.138</td>
</tr>
<tr>
<td>Plaque Thickness mm</td>
<td>4.5 (2.8-6.9)</td>
<td>4.1 (2.3-6.5)</td>
<td>0.288</td>
</tr>
<tr>
<td>FC Rupture</td>
<td>8 (42.1)</td>
<td>7 (17.5)</td>
<td><strong>0.043</strong></td>
</tr>
<tr>
<td>IPH</td>
<td>10 (52.6)</td>
<td>4 (10)</td>
<td>&lt;<strong>0.0001</strong></td>
</tr>
<tr>
<td>Large lipid core</td>
<td>12 (63.2)</td>
<td>16 (40)</td>
<td>0.096</td>
</tr>
<tr>
<td>Gd Enhancement</td>
<td>15 (78.9)</td>
<td>20 (50)</td>
<td><strong>0.034</strong></td>
</tr>
</tbody>
</table>
**S5. Supplementals Results:** Fibrous cap status and composition in the area of contrast enhancement depending on plaque types.

<table>
<thead>
<tr>
<th></th>
<th>Type 1 n=4</th>
<th>Type 2 n=8</th>
<th>Type 3 n=18</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC rupture n(%)</td>
<td>0</td>
<td>0</td>
<td>4 (22)</td>
<td>0.307</td>
</tr>
<tr>
<td>FC composition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loose fibrosis n(%)</td>
<td>1 (25)</td>
<td>8 (100)</td>
<td>9 (50)</td>
<td>0.009</td>
</tr>
<tr>
<td>Macrophage n(%)</td>
<td>2 (50)</td>
<td>3 (37.5)</td>
<td>3 (17)</td>
<td>0.288</td>
</tr>
<tr>
<td>Neovessels n(%)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>1 (6)</td>
<td>0.648</td>
</tr>
</tbody>
</table>