Endovascular management of symptomatic, vulnerable, hyperintense on post-contrast T1-weighted MR sequences carotid plaques: a 1-year single center experience

Poster No.: C-0780
Congress: ECR 2013
Type: Scientific Exhibit
Authors: R. Gandini, E. Pampana, D. Morosetti, A. Chiaravalloti, S. Fabiano, A. Bindi, G. Loreni, G. Simonetti; Rome/IT
Keywords: Interventional vascular, Neuroradiology brain, Vascular, CT-Angiography, MR-Angiography, Fluoroscopy, Stents, Angioplasty, Catheters, Acute, Embolism / Thrombosis, Arteriosclerosis
DOI: 10.1594/ecr2013/C-0780

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Ischemic stroke is responsible for 10% of all deaths and is the second cause of mortality worldwide; however, stroke is the leading cause of mortality in China and Japan (1). Carotid artery stenosis represents a major risk factor for stroke and transient ischemic attack (TIA) and it can determine approximately up to 25% of strokes (2). Histologic studies have shown differences between symptomatic and asymptomatic carotid plaques (3) and, consequently, carotid plaque evaluation has been focused on the identification of high risk carotid plaque patterns, as plaque ulceration, fibrous cap rupture or inflammation signs, instead of mere stenosis degree examination (6, 7). In this setting, in vivo High Resolution Contrast-enhanced MRI has been used to provide data regarding morphology and composition of human carotid plaque, thanks to its extensively histologically validated properties (6, 8-13). However, recent studies paid attention to inflammation within plaques, which stimulates the proliferation of vasa vasorum characterized by immature, thin-walled vessels prone to rupture and to progression to intraplaque hemorrhage and plaque rupture (14). Therefore a plaque characterized by inflammation and neovascularization by the vasa vasorum presents higher vulnerable nature compared to plaques with only high risk morphologic characteristics (15-20). In patients affected by a high risk carotid plaque, the first established therapy was surgical endarterectomy, even if carotid revascularization techniques have been undergoing a continuous less invasive evolution, mainly due to the development of new endovascular devices. Carotid artery stenting (CAS) has emerged as an alternative therapeutic option in patients who are considered at high surgical-risk due to co-existent medical co-morbidities or anatomical high-risk features (21-23). In this study we retrospectively evaluated the short term safety and the intermediate term efficacy in preventing cerebrovascular accidents of CAS in patients with highly inflamed vulnerable plaques, acute symptoms and high surgical risk, in order to validate the endovascular procedure as a safe and effective technique.
Methods and Materials

Patient selection and diagnosis.

Between January 2008 and December 2009, 102 patients (M/F 68/34) were referred to our institution for minor stroke or transient ischemic attack (TIA) risen up to one month before. The institutional review board at our institution gave full approval and waiver of informed consent for our retrospective study and approved our treatment protocol. All patients enrolled were at high surgical risk. At the hospitalization, patients underwent epiaortic vessels duplex ultrasound imaging (DUI) and magnetic resonance (MR) scan of the brain. Neurologic symptoms were assessed by a neurologist, who decided if patients should be considered symptomatic, namely when a hemispheric or retinal transient ischemic attack or a non-disabling stroke or retinal infarct arose within 30 days before first evaluation. Stenoses greater than 50% were reported in 31 patients (30.4%). Patients affected by stenoses smaller than 50% or characterized by symptoms determined by an etiology related to another cause from stenosis were excluded from the study. Patients presenting plaques determining stenoses greater than 50% underwent an instrumental in-depth evaluation with CT-angiography (31 patients, 100% of the whole patient cohort) in order to confirm stenosis degree and to obtain an objective and panoramic evaluation of the carotid plaque, anatomy of Willis circle and aortic arch for a correct pre-procedural planning. Also a HR-MRI evaluation (31 patients, 100% of the whole patient cohort) was performed and only the T1-weighted before and after contrast media injection was considered.

Plaque morphology on CT-angiography was defined as mostly lipidic with an Hounsfield unit (HU) <50, mostly fibrotic with an HU between 50 and 100 and mostly calcific with an HU >100. Among these patients, in 23 patients (71%) a mostly lipidic carotid plaque was diagnosed, in 8 patients (29%) the carotid plaques were characterized by a mostly fibro-calcific component. In patients who underwent a HR-MR examination, 19 carotid plaque showed a hyperintense signal on after-contrast T1-weighted images, while in 12 patients no significant contrast enhancement was pointed out.

CT acquisition protocol

CT exams were performed with a 64-slice CT scanner (LightSpeed VCT, General Electric Medical System, Milwaukee, WI, USA).

The acquisition stack extended from the ascending aorta to the intracranial circle in order to evaluate the anatomy and collateral vessels of the Willis circle for an eventual stop-flow protection device placement. A second image stack was then acquired after intravenous administration of iodinated contrast material using a dual-head automated injector (Stellant, MEDRAD, Pittsburgh, PA, USA). A dose of 80 ml of nonionic iodinated contrast material (Iomeron 400, Bracco, Milan, Italy) was administered through an 18-
gauge needle cannula placed in an antecubital vein, followed by a 40 ml of saline solution injection, both at a rate of 4 ml/s. To synchronize the acquisition start with the arrival of the contrast agent in the coronary arteries, the bolus-tracking technique was used. Parameters for the contrast-enhanced scan were beam collimation 64×0.625 mm, slice thickness 0.625 mm, reconstruction increment 0.625 mm, table feed 2.9 mm/rotation, tube rotation 0.35 s, tube voltage 120 kV, dose modulation protocol (intensity 140-750 mA), cranio-caudal scan direction. Scan duration was 8-10 s; adsorbed dose was 8-10 mSv.

**HR-MRI acquisition protocol**

HR-MRI exams were performed with a 3T MRI (Philips Achieva, Best, Netherlands) equipped with a sinergy multichannel faced array head and neck coil, using the following sequences:

- T1 weighted black blood sequence on axial plane pre and post contrast administration (TR: 1000 ms, TE: 20 ms, matrix 372x442, voxel size 0.43x0.43, FOV 160x193 mm, slice thickness 2 mm, NEX 1) focus on brain and neck acquisition
- T1 3D fast field echo (TR: 23 ms, TE: 3.5 ms, matrix 448x114, voxel size 0.33x0.66, flip angle 20°, NEX 2)
- Proton density weighted on axial plane (TR: 2000 ms, TE: 20 ms, matrix 264x258, voxel size 0.53x0.54, FOV 140x140 mm, slice thickness 2 mm, NEX 1)
- T2 weighted black blood sequence on axial plane (TR: 2000 ms, TE: 40 ms, matrix 264x248, voxel 0.53x0.56, slice thickness 2 mm, FOV 140x140 mm, NEX 1)

In our retrospective study we considered only the pre- and after-contrast media injection T1-weighthed images, in order to highlight plaques characterized by inflammation signs.

**CAS Procedure**

Thirty-one patients underwent to CAS procedure after the symptom onset. Nineteen CAS procedures were performed in selected patients affected by magnetic resonance evidence of hyperintense plaque on after-contrast T1-weighthed images. Patient cohort was characterized by 11 males (57.9 %) aged 75-90 years and 8 females (32.1%) aged 73-86 years. Twelve CAS procedures were performed in patients who didn't show any signs of hyperintensity within plaque on post-contrast T1-weighted, however affected by recent neurologic symptom onset needing and a stenosis greater than 70% an endovascular treatment. They were 9 males (75%) aged 74-91 years and 3 females (25%) aged 77-84 years.
Treatment protocols

Once obtained a morphological classification of the carotid plaque, patients were enrolled for an endovascular treatment. Written patient informed consent was obtained from each patient prior to intervention. Percutaneous treatment was performed in an endovascular suite. Aspirin (100 mg/day) and clopidogrel (75 mg/day) or ticlopidin (500 mg/day) were administered to the patients during three days previous the procedure. If this medical therapy couldn't be administered, patient received a loading dose of 500 mg aspirin and 300 mg clopidogrel before the intervention. 75 mg/day clopidogrel or 500 mg/day ticlopidin and 100 mg/day aspirin was continued for 45 days after stenting procedure. At the procedure beginning, adequate heparin was given to elevate activated clotting time to 300 seconds. A right trans-femoral approach was obtained and a 6 Fr 10 cm long introducer sheath was placed. To catheterize the right common carotid artery a 6 Fr 90 degree guide catheter (Boston Scientific, Natick, US) and an angle standard or stiff guidewire (Terumo, Tokyo, Japan) were used, while a 6 Fr 40 degree guide catheter allowed us to catheterize the left common carotid artery. A diagnostic angiography was performed to highlight the stenosis localization and degree following NASCET classification. In patients without any evidence of inflamed plaque an embolic protection device (EPD) (Epifilter, boston scientific, Natick, U.S.; Spider fx, Ev3; Emboshield, Abbott Vascular, Illinois, U.S.) was positioned in the distal portion of internal carotid artery and a self-expandable closed-cells or multisegment design stent device was used. In all patients previously examined, characterized by inflammation evidence, and consequently high embolization risk as short-term complication, a Mo.Ma ultra protection device (Medtronic Invatec, Roncadelle, Italy) was positioned through a 9 Fr femoral approach. The distal balloon of the device was inflated in external carotid artery with 5 ml contrast media and, afterwards, the proximal balloon in common carotid artery until flow was stopped. A self-expandable closed-cells or multisegment design stent device (Wallstent, Boston scientific, Natick, U.S.; Cristallo Ideale, Medtronic Invatec, Roncadelle, Italy; X-Act, Abbott Vascular, Illinois, U.S.) was advanced over the 0.014 in guidewire. Stent sizes were chosen on the basis of preprocedural CT evaluation. At the end of the procedure the filter was collapsed and removed, while, in patients with Mo.Ma. ultra device placement, the blood in internal carotid was aspirate by three 20 cc syringes in order to remove accidental atheromatous debris; afterwards the distal balloon was deflated at first, followed by the deflation of the proximal balloon. In all procedures the angioplasty wasn't performed either before or after stent deployment to decrease embolization risk. Technical success was defined as stent deployment with residual stenosis not exceeding 30% of physiologic vessel diameter in absence of alteration of cerebral circulation.

Follow-up
All patients were examined by an expert neurologist before and after the procedure. Main technical complications were defined as dissection, vessel rupture, thrombosis and occlusion. Main clinical complications were defined as major stroke, minor stroke, TIA, myocardial ischemia and death. Neurologic complications were evaluated following National Institutes of Health Stroke Scale (NIHSS) (16) as clinical assessment and through the use of MRI with diffusion weighted sequences (DWI) and perfusion-weighted sequences (PWI) as instrumental evaluation. Major stroke was characterized by an event characterized by NIHSS increase greater than 3 for a period longer than 24 hours; minor stroke was defined by an increase less than 3. Hemodynamic parameters were monitored during the post-procedural 4 hours. Patients were discharged after a mean period of five days after the endovascular procedure. DUI was performed at 1, 3, 6 and 12 months during follow-up period to evaluate treatment results. CT- or MRI-Angiography was indicated when DUI highlighted neointimal hyperplasia or hemodynamic alteration inside the stent.

**Statistical analysis**

All data were entered into a database for statistical processing. Data were expressed as means plus one standard deviation (SD) or as percentages. The comparison between groups was obtained using the Fisher exact test for categorical variables while t Student test was applied for continuous variables, as appropriate. Statistical significant was set at p<0.05. All statistical analysis were performed using the software *Epi Info 3.5.1* (CDC, Atlanta USA).
Fig. 1: Fig 1 (A) Duplex ultrasound evaluation reporting a hypoechoic plaque on antero-medial side of the right internal carotid wall. CTA scan, (B) in axial plan and (C) in Volume Rendering reconstruction, confirming a hypodense area, related to high lipid rich plaque. (D-E) Axial T1 weighted HR-MRI images, showing hypointense plaque, enhancing on (F-G) T1-weighted images after contrast media injection (Dotarem).

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Fig. 2: (A) Angiographic evaluation of carotid plaque showed in Fig. 1. (B) Mo.Ma. protection device placement and (C) stent release. (D) Post-procedural angiographic evaluation after Mo.Ma. retrieval, showing satisfying vessel lumen diameter restore.

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<table>
<thead>
<tr>
<th></th>
<th>group 1</th>
<th>group 2</th>
<th>P value</th>
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<tr>
<td>Median age</td>
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<td>81 ± 4.9 years</td>
<td>1.96^a</td>
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<td>Males</td>
<td>11 (57.9 %)</td>
<td>9 (75 %)</td>
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<td>Coronary artery disease</td>
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<td>5 (41.6 %)</td>
<td>0.242^b</td>
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<td>12 (63.1 %)</td>
<td>1 (8.3 %)</td>
<td>0.035^b</td>
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<tr>
<td>Hypertension</td>
<td>6 (31.6 %)</td>
<td>12 (100 %)</td>
<td>0.041^b</td>
</tr>
<tr>
<td>Current or previous smoke habit</td>
<td>6 (31.6 %)</td>
<td>4 (33.3 %)</td>
<td>0.287^b</td>
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<tr>
<td>Diabetes mellitus</td>
<td>8 (42 %)</td>
<td>4 (33.3 %)</td>
<td>0.263^b</td>
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<tr>
<td>Complications</td>
<td>1 (5.3 %)</td>
<td>0 (0 %)</td>
<td>0.625^b</td>
</tr>
<tr>
<td>Stenosis degree (%)</td>
<td>69.9 ± 4.5</td>
<td>78.7 ± 4.5</td>
<td>1.96^a</td>
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</tbody>
</table>

Fig. 3: Table I: Characteristics of population who underwent a endovascular procedure after the defined diagnostic path. Significant statistical difference was defined as P
Results

Before the procedure all patients were matched following the criteria present in table I and divided in two different groups. In group 1 characterized by 19 patients with hyperintense plaque on after-contrast T1-weighted images, 12 stenoses (63.1%) were located in the right internal carotid artery, 7 (37.9%) in the left internal carotid artery. The degree of stenosis averaged 67 ± 6%, in particular stenoses >70% were found in 10 patients (52.6%) and stenoses averaged from 50 to 70% were found in 9 patients (47.4%). In all symptomatic patients the carotid plaque with the characteristics of inflammation was situated on the same side where direct and indirect signs of brain suffering were present. In only one (5.2%) patient bilateral inflamed plaques were diagnosed, however it was decided to treat the lesion which was related to the clinical symptomatology and to the MR findings, which was characterized by a higher stenosis degree, while the contralateral stenosis, which was equivalent of 55% stenosis degree, was treated in a following endovascular treatment and isn't considered in this study. Twelve patients (63%) with inflammation signs in the HR-MR examination, presented dislipidemia, with very high levels of Low Density Lipoprotein (LDL) and cholesterol. In only one patient of the group 2 dyslipidemia was noted (p<0.05). In all patients corresponding to group 2 a high blood pressure was evaluated compared to six patients of group 1 (P<0.05).

In two patients a type II aortic arc was present and a "shuttle" guided catheter was necessary in order to achieve higher stability and better control over the dedicated devices. After Mo.Ma protection device disassembly, atheromatous debris was found in the basket in 11 patients (57.9%). In patients in which atheromatous debris was visible in the filter basket, other two additional 20 cc of syringes of blood were aspirated with no debris detected at the end of the procedure. In all procedures no significant residual stenosis (residual stenosis > 30%) resulted.

In group 2 characterized by 12 patients without any signs of inflamed plaque, 9 (75%) were located in the right internal carotid artery, 3 (25%) in the left internal carotid artery; the degree of stenosis averaged 78.7 ± 4.5%, with 10 patients (32.2%) who presented stenoses >70% and 2 patients (6.4%) with stenoses averaged from 60 to 70%. No atheromatous debris were found in the filter at the end of the procedure in group 2.

Technical success was obtained in all procedures (100%). No technical complications occurred at the end of the procedure. One TIA (5%) was observed in the group of patients treated with Mo.Ma filter protection device, likely related to hypoperfusion caused by the device. In this patient an MRI examination with Diffusion Weighted Imaging and ADC map was immediately performed and no signs of acute ischemia were identified. No major adverse cerebrovascular events in hospital-stay and at 30 day follow-up were observed in group 2 of patients. There wasn't a statistical differences in the complication incidence between the two groups of patients (P<0.05). Neither periprocedural death nor myocardial infarction occurred. Clinical follow-up data and DUI at 30 days, 3, 6 months, and 1 year
were obtained and all implanted stents remained patent. Mean procedure time was higher in procedures in which Mo.Ma. protection device was deployed (procedure with Mo.Ma. protection device lengthened of 8 ± 1.3 minutes).
Conclusion

Ischemic stroke is responsible for 10% of all deaths and is the second cause of mortality worldwide. Carotid artery stenosis is the major risk factor for this disease (1). The degree of luminal stenosis has been used for years as a marker of atherosclerotic stage, and as an indication for surgical or endovascular intervention (6).

However several studies have underlined the importance of broadening the horizons of stenosis criteria: in this respect clinical trials have shown that a considerable population of patients which are symptomatic for transient ischemic attack or stroke have mild to moderate carotid stenosis, and consequently the severity of carotid stenosis remains a poor discriminator of stroke risk (7).

The risk of considering only stenosis criteria implies that a great population of patients would be considered to have early-stage carotid plaques, despite the high risk of morbidity (6, 25).

During last years, histological studies emphasized the fact that many morphological characteristics such as lipid necrotic core, thin fibrous cap, intraplaque hemorrhage and neovasculature can be related to a high embolization risk plaque, which is described as "vulnerable plaque" (6, 26-29). However recent studies reported an embolization risk related to lipid content not statistically associated with symptomatic lesions and showed active plaque inflammation as major criteria of vulnerable nature (15,16,19). In fact, inflammatory cells within the plaque might cause directly the degradation of all extracellular matrix components, hypoxic stimuli and formation of vasa vasorum in atherosclerotic lesions. The intraplaque vasa vasorum are characterized by immature, thin-walled vessel with high risk of microvessel collapse and progression into more advance plaques. These lesions are at high risk for intraplaque hemorrhage and plaque rupture (14,15,17,18,20).

High-resolution magnetic resonance imaging (MRI) is the most promising technique to obtain carotid atherosclerotic plaque evaluation. In fact MR allows direct vessel wall examination thanks to its excellent soft tissue contrast, sensibility in plaque morphology characterization and inflammation degree evaluation, which can potentially monitor the progression of the disease (6,7). Cai et al used unenhanced T1W and contrast-enhanced T1W images to measure the intact fibrous cap, showing a moderate to good correlation between the MR findings and excised histological specimen (6, 7, 13). Contrast media injection allows to diagnose the inflamed plaques and can highlight vascular supply, neovasculature growth and increased endothelial permeability within the carotid plaque (6, 7, 20,30).

All these considerations are useful because inflamed plaque findings with a recent onset of symptoms inevitably raises
the attention to the plaque itself as the cause of these events in acute. Moreover inflamed plaque characteristics can be potentially diagnosed by only pre- and after contrast media injection T1-weighted, reducing examination acquisition time in patients with recent symptoms onset.

To date this is the first study in which there is a comparison between symptomatic patients with high surgical risk characterized by hyperintense plaque on after contrast T1-weighted images compared with those characterized by absence of hyperintense plaque, trying to differentiate patients with recent tromboembolic event from those with hemodynamic onset of symptoms. This new approach in investigating atherosclerotic carotid plaque is also a challenging issue for treatment, because it has the capability of identifying not only symptomatic patients but also patients with highly inflamed plaque, considered as a "pitfall" because of the unsettled surgical-endovascular management (31). Moreover our evaluation allowed us to make different choices on device deployment in the endovascular procedure based on HR-MR examination.

Many hospital structures continue to prefer a surgical treatment to remove the highly inflamed plaque or plaque composed of lipid-rich necrotic core, irrespective of a degree of luminal stenosis (9, 18), considering the endovascular procedure as secondary choice in patients with high comorbidities and contraindications to surgical approach. In fact, our population cohort was characterized by high surgical risk patients, with endovascular treatment being the therapeutic option with the highest benefit/risk ratio.

In this perspective, the choice of the appropriate device to deploy is fundamental. Nevertheless, assessment of stent design and filter protection device placement represents a controversial point.

Concerning stent strut, some authors, as Schillinger et al., reported a non-significant statistical difference between the closed- and open-cell stents. However, according to Hart et al., an increased coverage of vessel plaque, with the exclusion of its surface from the blood flow, remains an established concern for carotid artery stenting (31, 32). This concept is mentioned also by Boisier et al, who underlined a higher percentage of complication in the after-procedural period, compared to the procedural time where a filter protection is placed (34, 35). In this condition closed-cell stents represent the best option to obtain a plaque material scaffolding in the vessel wall in order to reduce complication rates, which are higher in high risk patients with a device characterized by a larger free cell area (33-35).

Also the cerebral protection device represents a doubtful question. Though for years the use of a filter protection device represented a fixed point, several studies produced controversial results. As reported by Tietke et al. in their review, the filter protection device may not eliminate periprocedural embolic events, but it may potentially enhance the risk of periprocedural complications, especially during its placement (37). Nevertheless some authors reported opposite results (36). In case of stop-flow protection devices, as Mo.Ma, it has been demonstrated that they reduce atheromatous debris embolization.
during stent deployment, demonstrating it with transcranial Doppler, especially for debris minor than 100µm, small enough to pass through the filter but large to occlude arterioles and capillary beds (33, 38). Moreover, this protection device avoid guidewire passage through the stenosis while the blood flow isn't stopped (33). In the latter fashion the authors can avoid any thrombo-embolism event during the guidewire passage and the unprotected predilatation, which coincide with 20 % of the microembolic signals during each endovascular phase (33, 39, 40). The high percentage (57.9 %, 11 over 19 total patients) of embolic debris encountered in our series strengthensthe hypothesis that inflamed plaques have an high embolization risk. However in patients who should undergo an endovascular procedure with a stop-flow protection device placement, intracranial vascularization and contralateral carotid anatomy has to be evaluated in order to examine the device tolerance. Other limits are represented by the high device cost and the high learning curve.

Our study was, thus, aimed to identify patients with contraindications to CEA characterized by inflamed plaques with the subsequent devices choice, as closed-cell or modulated stents and proximal protection devices, deployed specifically in order to prevent microembolic accidents.

The main limits of this retrospective study is the relatively small number of subjects and the retrospective nature of our study which need to be confirmed by a large randomized studies.

Nowadays the availability of HR-MRI, as an "in vivo" alternative characterization of plaque morphology and its intrinsic structure, can lead to the identification of highly inflamed plaques which need to be treated urgently.

The absence in our experience of significant complications rate may evidence not only that CAS can be considered an alternative treatment also for highly unstable plaques, usually treated by CEA, but also that this evidence may be a result of an accurate identification of inflamed plaques through morpho-structural evaluation obtained by HR-MRI, with a subsequent adequate stent and cerebral protection device choice.

We, thus, firmly believe that, in order to perform a correct endovascular treatment of high-risk, inflamed atherosclerotic plaques, an accurate imaging evaluation is mandatory.
References


14. ten Kate GL, Sijbrands EJ, Valkema R, ten Cate FJ, Feinstein SB, van der Steen AF, Daemen MJ, Schinkel AF. Molecular imaging of inflammation...


