Aortic arch and common carotid artery plaques with soft components pose a substantial risk of cerebral embolization during carotid stenting

Péter Szikra¹, Erika Vörös¹, Krisztina Boda², Ferenc Rarosi², Attila Thury³, Pál Barzó⁴ and Tamás Németh⁴

Abstract
Objectives: A higher rate of embolization is considered a disadvantage of carotid stenting (CAS), when compared with carotid endarterectomy. Plaques in the aortic arch (AA) and the common carotid artery (CCA) may be additional sources of embolization to stented internal carotid plaques during CAS. In this study, we aimed to investigate the relationship between these plaques and intracerebral embolization.

Methods: We analyzed the occurrence and composition of plaques in the AA and CCA by computed tomography angiography (CTA) in 101 consecutive cases of CAS. Cases of peri-procedural embolization were detected on diffusion-weighted imaging as lesions demonstrating diffusion restriction. We applied the χ² and Fisher’s exact tests, as well as logistic regression models.

Results: The occurrence of plaques in the AA and CCA was significantly related to the appearance of new diffusion-weighted imaging lesions (p = 0.013 and p = 0.004, respectively). Patients with soft plaques in the AA or CCA had a significantly higher risk of embolization than those without plaques (p = 0.012 and p = 0.006, respectively). In contrast, homogeneously calcified plaques did not pose significantly higher risks.

Conclusions: Soft plaques in the AA and CCA result in a substantial risk of embolization during CAS. Use of a CTA examination of the AA and the CCA in patients with carotid stenosis may help to select lower-risk patients for CAS.

Keywords
Aortic arch, arterial plaque, calcified plaque, carotid artery, carotid stenting, carotid stenosis, cerebral embolism, computed tomographic angiography, diffusion-weighted imaging, embolism, risk factors, soft plaque

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Introduction
When carotid artery stenting (CAS) is carried out by an experienced interventionalist, it is equivalent to carotid endarterectomy (CEA) performed by an experienced surgeon.¹ Recent comparative studies have shown that CAS and CEA are associated with similar cumulative morbidity and mortality rates; however, while peri-procedural embolization is more frequent in stenting, surgery carries a higher risk for acute myocardial infarction, surgical infection and complications of anesthesia.¹,²

Reducing the risk of peri-procedural embolization related to CAS might increase its applicability, considering that this technique can be carried out without anesthesia. After CAS, fresh ischemic lesions frequently occur, not only in areas supplied by the vessel affected by CAS treatment, but also on the contralateral side and in the posterior fossa. The appearance of these lesions cannot be attributed to the stented plaque.³

Ulcerated plaques of the aortic arch (AA) have an important role in the development of ischemic stroke as a source of embolization.⁴ Therefore, development of fresh ischemic lesions in the course of CAS is unlikely to be explained by the presence of only internal...
Computed tomographic angiography (CTA) is a suitable and accepted imaging method for the examination of atherosclerotic plaques regarding spatial position and composition. This technique even enables the mapping of sections of vessels that are not accessible by ultrasound. Diffusion-weighted imaging (DWI) is used to locate the positions of new ischemic lesions resulting from intervention, and assesses their sizes (i.e. the consequences of dislodged emboli by the manipulation of catheters).

In this study, we examined whether there are relationships between AA and common carotid artery (CCA) plaques in the development of fresh ischemic lesions. We also examined whether the composition of plaques affected the degree of embolization. The results of our study were expected to help select patients with carotid stenosis in whom the application of the endovascular technique is accompanied by a low risk of embolization and thus, for whom stenting may be recommended.

Materials and methods

This study was conducted with the approval of the Board of Ethics of the University of Szeged’s Medical University Centre. All of the patients were fully informed about the study and provided written consent.

Between June 2010 and December 2012, a total of 101 consecutive cases involving 92 patients with symptomatic carotid stenosis (40 women and 52 men; mean age 64.8 ± 8.2 years) were examined retrospectively at our institution (Table 1).

The CTA procedure was carried out with a 64-slice scanner (GE Light Speed VCT, General Electric Healthcare, Fairfield, CT, USA) in accordance with the following protocol:

- Helical mode, gantry rotation: 0.4 s;
- Collimation: 62 × 0.625 mm;
- Pitch: 0.984:1;
- Section thickness: 0.625 mm;
- Reconstruction interval: 0.5 mm; and
- Acquisition parameters: 120 kV/50–600 mA.

The examination was carried out in the caudocranial direction, from the middle of the chest up to the vertex. A volume of 50–70 ml of contrast medium (Omnipaque 350, General Electric Healthcare, Fairfield, CT, USA) was injected through the antecubital vein with an injector, at a rate of 2.5–4 mL/s. The test bolus technique was applied to optimize the timing of the CTA.

Table 1. Patient demography.

<table>
<thead>
<tr>
<th>Case number</th>
<th>101</th>
</tr>
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<tbody>
<tr>
<td>Patient number</td>
<td>92</td>
</tr>
<tr>
<td>Mean age/year</td>
<td>64.8 ± 8.2</td>
</tr>
<tr>
<td>Female gender</td>
<td>40  43.50%</td>
</tr>
<tr>
<td>Male gender</td>
<td>52  56.50%</td>
</tr>
</tbody>
</table>

Measurements of stenosis were taken with the Advanced Vessel Analysis program, based on a decrease in the cross-sectional area.

CTA images showed the presence or absence of plaques in the AA and CCA – brachiocephalic areas. Two groups of plaques were distinguished: The purely calcified and the partly or purely soft plaques. In most cases, proper window use (our settings were window width 500–900 HU and window level 100–250 HU) enabled the calcified and soft plaques to be distinguished by visual assessment. When the material of the plaque was in doubt, its density was measured. Plaques with a density over 241 HU were regarded as calcified; while those below 240 HU were regarded as soft. We performed the density measurements on the source images, with the Measure program viewer and display tools of Advantage Windows 4.4 (General Electric Healthcare).

CAS was carried out under double thrombocyte aggregation protection (aspirin 300 mg/d and clopidogrel 75 mg/d), that were started at least 3 days before endovascular intervention. At the start of the intervention, 70 U/kg heparin was administered in a bolus. Whenever significant bradycardia or asystolia was noted during the post-dilation phase, the required amount of atropine was injected.

Only the vessels that were affected by stenosis were selectively examined with catheter angiography. As a first choice, we used the head-hunter 1 type, and in the case of a failed attempt, the Simmons 1, 2 or 3 type 4F catheter (Cordis, Johnson and Johnson, East Bridgewater, NJ, USA), introduced by a 035° Standard Glidewire (Terumo, Somerset, NJ, USA) guide wire. In the case of any difficult morphological situation, we used a 035° × 260 replacement wire, the Emerald guide wire (Cordis). For pre-dilation and post-dilation, we used a 0.014" 4 × 20 mm and 6 × 20 mm Aviator Plus (Cordis) balloon catheter, respectively. No embolic protection device (EPD) was used in the interventions. Two types of closed-cell stents were implanted: The Carotid Wallstent (Boston Scientific, Natick, MA, USA) and the Xact Carotid Stent (Abbott Laboratories, Abbott Park, IL, USA).

All stent procedures were done under local anesthesia, with monitoring by an anesthesiologist. All stenting procedures were performed by the same neuroradiologist, with experience in > 800 carotid stenting.
procedures. Transfemoral arterial approaches were performed in all cases. We did a diagnostic angiogram of the common carotid artery in question, to confirm the presence of significant stenosis and to make the final decision to do the interventional procedure. All stents were post-dilated to not less than 90% of the measured diameter of the normal ICA. Finally, angiograms of the carotid bifurcation and the intracranial circulation were performed, to demonstrate the reconstruction of the carotid lumen and to exclude macroembolic complications. After the procedure, the patients were monitored in a neurologic intermediate care unit for 24 hours.

New ischemic lesions were detected with DWI and the apparent diffusion coefficient (ADC) mapping was performed the GE Signa Excite HDxT, 1.5T (General Electric) and Advantages Windows 4.4 workstation, within 48 h of the intervention. DWI was acquired with an echo-planar axial sequence as follows:

- Repetition time: 8000 ms;
- Echo time: minimum 97.6 ms;
- Matrix: 128 × 128 matrix;
- FOV: 260 × 260 mm;
- Slice thickness: 5 mm without a gap; and
- Choosing b values of 0 and 1000 s/mm².

An ADC map was generated with the Functool program on the Advantage Windows workstation in each case. Areas showing restricted diffusion of a high signal on DWI and a low signal on an ADC map were identified as new ischemic lesions. Depending on localization, lesions were assigned to three groups: ipsilateral, contralateral and posterior fossa. The lesions were grouped by size (<10 mm, 10–20 mm and >20 mm). The observer analyzing CTA was blinded to the results of DWI. The CTA, DWI examinations and stenting procedure were always carried out by the same neuroradiologist, who is a professional with 20 years of experience.

The period between the first femoral puncture and the end of the first 48 h following revascularization was regarded as the peri-procedural period of the intervention (Figure 1).

**Statistical methods**

Patients with plaques in the AA and CCA were compared with those without such plaques, to determine which group had more chance of developing new ischemic lesions. The relationships between the occurrence of plaques and new ischemic lesions was analyzed with the χ² test and Fisher’s exact test. Logistic regression models were applied for assessing the effect of the risk factors. The effect of the composition of plaques in the AA and CCA on the risk of appearance of new ischemic lesions was measured by ORs. Additionally, 95% CI for the ORs were calculated. P values < 0.05 were regarded as statistically significant. The statistical analysis was carried out with SPSS 22 software (IBM SPSS Statistics for Windows, Version 22.0.)

**Results**

All 101 carotid stenoses were successfully treated with endovascular treatment. Two cases developed clinical signs of peri-procedural ischemic stroke (modified Rankin Scale 2 and 3). New ischemic lesions were found in 50% of all cases (50/101). In 19% (19/101) of the cases, only one new ischemic lesion occurred. The sizes of new ischemic lesions did not exceed 10 mm in 90.8% of cases. Therefore, those lesions exceeding 10 mm were not studied as a separate group. The average procedure time was 58.8 (35–115) minutes. The average procedure time of patients without a new DWI lesion was shorter (57.2 minutes), while the procedure time of the cases with new DWI lesions was numerically longer only (60.32 minute). The difference was not significant. In 12% (12/101) of the failed attempts at entering via the first choice diagnostic catheter, a second diagnostic catheter was used. New DWI lesions were identified in 75% (9/12) of these cases. A total of 76% (38/50) of these new lesions occurred in areas that were supplied by vessels affected by the treatment (ipsilateral side). A total of 24% of the new lesions (12/50) were not related to the treated stenotic lesion (contralateral side and/or posterior fossa). In 42% (21/50) of the cases where new ischemic lesions were present, embolization occurred on the ipsilateral side and on the contralateral side and/or the posterior fossa.

The incidence of new ischemic lesions was statistically not independent of whether the AA was covered by plaques. A significant (p = 0.013) relationship was found between the occurrence of plaques covering the AA and the incidence of new ischemic lesions. Where the AA plaque was purely calcified, the occurrence of a plaque resulted in a 2.311 times higher risk (OR) of embolization, compared with plaque-free cases; but this increase was not significant (p = 0.28; 95% CI 0.505–10.573). For patients with plaques containing soft components, the increase in risk was 5.617 times, compared with plaque-free cases (p = 0.012; 95% CI 1.453–21.713) (Table 2).

When comparing cases of purely calcified plaques in the AA with those containing soft components, the OR for the risk of developing new ischemic lesions was 2.431; however, this result was significant only at a significance level of 10% (p = 0.08).

The incidence of new ischemic lesions was statistically not independent of whether the CCA was covered by plaques. A significant (p = 0.004) relationship was found between the plaques covering the CCA and the incidence of new lesions. If the plaques in the CCA were purely calcified, they did not cause any further increase in risk (OR 0.812), compared with patients with no plaques (p = 0.67; 95% CI 0.3135–2.111).
When the CCA plaque contained soft components, the risk of incidence of new ischemic lesions was 4.411 times higher, as compared with patients without plaques ($p = 0.006; 95\% \text{ CI } 1.517–12.822$), as seen in Table 3.

When comparing purely calcified plaques in the CCA with those containing soft components, the OR for the risk of developing new ischemic lesions was 5.429 ($p = 0.003$). When the patient represented both AA and CCA plaque that contained soft components,
the risk of incidence of new ischemic lesions was 7.037 times higher, as compared with patients without plaques ($p=0.0003$; 95% CI 2.364–20.944).

**Discussion**

In the current study, we found new ischemic lesions in 50% of all CAS cases that we detected. This rate is higher than that in cases of CEA treatment (24–34%); but it is similar to previous results of CAS treatment, despite the use of embolic protection device (38–67%).12,17–20 We found that not all new ischemic lesions can be regarded as related to the area of the vessel that has undergone treatment, because lesions were also found in 24% of cases on the contralateral side and/or in the posterior fossa. These findings correspond well with those observed in previous clinical studies.2,21,22

Yoshimura et al.4 identified ulcerated plaques in the AA as a source of embolization that could be related to the development of ischemic strokes. The findings of Kim et al.3 suggest that maneuvers in the AA during CAS play an important role in the occurrence of new ischemic lesions in the posterior fossa and contralateral ICA territory. There is a difference between purely calcified plaques and those containing soft components in their potential to produce emboli. Therefore, the composition of plaques can be a factor involved in cases with plaques in the AA and CCA.11,23–27 No EPD was used in the interventions: At present there is no available level 1 evidence to support the routine use of EPDs.28–31 While during part of the peri-procedural phase an EPD may provide partial protection of the ICA to be treated, it does not provide protection against contralateral or posterior fossa embolization originating from the plaques of the AA on which our study was focused. Unfortunately, at present we have no device restricting embolization that could provide protection during diagnostic catheter use or the introduction of the thickest endovascular device, a guiding catheter, for both the vessel area that is to be treated and for the areas subject to embolization by the AA and CCA plaques.

We used CTA to distinguish calcified plaques from soft plaques, based on density.5–10 We did not investigate soft plaques further. This is because according to studies by Wintermark et al.6 and De Weert et al.8 the density values of the soft components, such as necrotic tissue, other tissues rich in lipids, connective tissue and plaque hemorrhage show considerable overlap. Therefore, they are collectively referred to as a ‘soft plaque’.6,8 For detecting new ischemic lesions, we applied the internationally accepted method of DWI.11–14 Most areas of restricted diffusion cause no neurological symptoms (i.e. they are functionally silent ischemic areas).3 In our study, although new ischemic lesions were detected in 50% of all cases, only 2% of these DWI lesions were found to be symptomatic; however, many studies have shown an association between new asymptomatic ischemic lesions and worsening results of neuropsychological tests.13,32 Gensicke et al.33 showed that ischemic brain lesions discovered on DWI after CAS appear to be a marker of increased risk for recurrent cerebrovascular events. Therefore, minimizing the risk of embolization should be a priority.

In our study, we found that there was a relationship between the presence of AA plaques and development of fresh ischemic lesions. Embolization in an area other than that supplied by the stented ICA occurred in 24%
of all cases, which is slightly less than the results of a similar study of 32 patients (41%)\(^0\); however, this finding emphasizes the need to further investigate the potential of plaques in the AA to produce emboli.

In our study, not all of the patients whom received CAS treatment had plaques in the AA or CCA. In cases where no plaques were present in the AA, we did not encounter any new lesions outside the territory supplied by the vessel in question. This lack of finding confirms our notion of new contralateral and posterior fossa ischemic lesions originating in the AA. AA and CCA plaques significantly increased the risk of development of new ischemic lesions, compared with cases where AA and CCA plaques were not present. In cases where the AA plaque was purely calcified, no significant difference in the incidence of new ischemic lesions was detected. When patients with purely calcified AA plaques were directly compared with those who had plaques with soft components, the risk of developing new ischemic lesions was not significant \((p = 0.08)\). The lack of significance is thought to be due to the moderate sample size. We found that there was a relationship between the presence of CCA plaques and the development of fresh ischemic lesions. When patients with purely calcified CCA plaques were compared with those with plaques with soft components, the risk of developing new ischemic lesions was significant. These results suggested that plaques with soft components in the AA and CCA had an increased risk of peri-procedural embolization. Use of a smaller, more properly-shaped device in the AA decreases the mobilization of atheromas.\(^3\) One of the reasons for patients suffering an embolism during intervention is related to manipulation of the catheter during the procedure.

The AA and CCA form part of the intervention route that is used in the course of ICA stenting, where the guide wires and catheters come into contact with and mechanically insult the vessel walls with plaques on them. Therefore, both of these areas are assumed to increase the rate of complications of embolization in CAS. While plaques in the AA can also affect the contralateral side and the posterior fossa, plaques in the CCA can only affect the ipsilateral side, because of anatomical reasons; however, it should be noted that the use of an inflated flow reversal EPD in a plaque-covered CCA raises questions, in view of the results of this study. The CCA plaque definitely deserves to be studied in the case of the most up-to-date flow reversal devices inserted directly into the common carotid artery, the Silkroad system (Silkroad Medical, Sunnyvale, CA), where a small incision is performed on the CCA and the loop is placed to clamp the artery.

Even when using 4F soft diagnostic catheters, a neurological complication rate of 1.3% should be expected, as shown by a prospective study of diagnostic cerebral angiograms of 2899 patients.\(^3\) The interventionalists navigate instruments by rotating and pushing forward, and by withdrawing the guide wire and a 5–8F-diameter catheter towards the ICA stenosis.

The catheter always rests on the inside surface of the vessel wall, where it exerts some force, depending on the morphology of the vessel and flexibility of the catheter on the point that supports them. The force exerted on the points supporting the catheter increases as a result of the changes in vessel morphology and a decrease in the radius of its bends.\(^3\)

New peri-procedural ischemic lesions appearing on the contralateral side or in the posterior fossa are highly likely to be the consequence of manipulations of the catheter in the AA.\(^3\) Therefore, extending CTA mapping to the AA is important. CTA mapping of potential embolized plaques to decrease the complications of embolization in patients may help make catheter therapy a safer treatment, even if there are plaques in the AA.\(^9\)

**Conclusions**

Soft plaques in the AA and CCA significantly increase peri-procedural embolization in treatment-related and non-treatment-related locations; however, in cases where purely calcified plaques or no plaques are present, performing endovascular procedures in the ICA did not result in any increase in risk. Use of a CTA examination of the AA and the CCA in patients with carotid stenosis may help to select lower-risk patients for CAS. One of the limitations of this study was that it is a retrospective one; therefore, more patients should be involved in future studies in order to produce more detailed results.

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