ADC mapping of chronic cerebral hypoperfusion induced by carotid artery stenosis

Cartographies ADC de l'hypoperfusion cérébrale chronique induite par une sténose de l'artère carotide


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KEYWORDS
Carotid stenosis; Magnetic resonance imaging; Diffusion-weighted imaging; Apparent diffusion coefficient; Ischemia

Summary
Background. — Carotid artery stenosis is associated with the occurrence of acute and chronic ischemic lesions that increase with age in the elderly population. Diffusion Imaging and ADC mapping may be an appropriate method to investigate patients with chronic hypoperfusion consecutive to carotid stenosis. This non-invasive technique allows to investigate brain integrity and structure, in particular hypoperfusion induced by carotid stenosis diseases. The aim of this study was to evaluate the impact of a carotid stenosis on the parenchyma using ADC mapping.

Methods. — Fifty-nine patients with symptomatic (33) and asymptomatic (26) carotid stenosis were recruited from our multidisciplinary consultation. Both groups demonstrated a similar degree of stenosis. All patients underwent MRI of the brain including diffusion-weighted MR imaging with ADC mapping. Regions of interest were defined in the anterior and posterior paraventricular regions both ipsilateral and contralateral to the stenosis (anterior circulation). The same analysis was performed for the thalamic and occipital regions (posterior circulation).

Results. — ADC values of the affected vascular territory were significantly higher on the side of the stenosis in the periventricular anterior (P < 0.001) and posterior (P < 0.01) area. There was no difference between ipsilateral and contralateral ADC values in the thalamic and occipital regions.
Introduction

Carotid stenosis is associated with an increased risk of acute and chronic infarction [1]. At 2 years of follow-up, the risk of a new stroke is 28% for symptomatic stenosis of 70—99% and 13% for stenosis of 50—69%.

Carotid endarterectomy is now well-established as a way to prevent infarction in symptomatic carotid stenosis patients. The benefit is lower for symptomatic stenosis between 50 and 70% and higher for stenosis of a grade of 70% [2]. For asymptomatic patients, carotid endarterectomy has a benefit for patients younger than 75 years old with a stenosis of about 70% or more on ultrasound [3].

Carotid stenosis may induce a chronic hypoperfusion. To assess changes in brain perfusion in carotid disease, a number of techniques have been used such as parenchymography [4] and CT perfusion [5]. Diffusion-weighted MR is a technique that images the molecular motion of tissue [6,7], which allows for the acquisition of a measure of fractional anisotropy [8]. This technique has been extensively used in stroke [9–11] and in degenerative conditions [12], as well as in the monitoring of therapy [13,14]. From the diffusion-weighted MR images, an apparent diffusion coefficient (ADC) can be calculated. Elevation of this ADC has been associated with vasogenic edema.

There are few studies that have used the ADC values to evaluate the impact of a carotid stenosis on the parenchyma. Sionne et al. [15,16], using diffusion-weighted MRI, found increased ADC in 42 patients with carotid stenosis on the ipsilateral side of the stenosis. The authors argue that the increased ADC may be associated with leukoaraiotic development (preleukoaraiosis).

Leukoaraiosis is seen on T2-weighted MR images as hyperintensity. It is frequently observed in the periventricular cerebral white matter and increases with aging. The relationship between leukoaraiosis and carotid stenosis is unclear: Streifler et al. studied 2618 patients from the NASCET study and diagnosed only 493 with leukoaraiosis [17]; they found no relationship between severity of stenosis and severity of leukoaraiosis. Patients with more extensive leukoaraiosis, however, were found to have a worse prognosis [17].

In the current study, we measured ADC values using MRI diffusion to assess the effect of chronic hypoperfusion on ipsilateral and contralateral hemisphere brain tissue in patients with carotid stenosis.

Methods

The study has been approved by the local ethics committee (Protocol 06-039 [NAC 06-011]). All patients were recruited from the carotid stenosis board of our institution, where patients are seen by a multidisciplinary panel comprising neurologists, neurosurgeons, cardiac surgeons, angiologists, cardiologists and neuroradiologists.

We included 59 patients aged between 46 and 97 years (mean: 73.64, SD: 11.61; 24 women and 37 men). They were recruited between 2006 and 2010, and all underwent MRI of the head and neck. In our population, 33 patients were symptomatic and 26 were asymptomatic. The mean age of the symptomatic group was 75 years old and 72.7 for the asymptomatic group (P = NS). The percentage of stenosis was between 60 and 90% (mean 80, SD: 8.4). Twenty-nine patients had stenosis on the right side and 30 on the left. Fifty-one patients had at least one cardiovascular risk factor most often hypertension, diabetes, or dyslipidemia (see Table 1).

<table>
<thead>
<tr>
<th>Table 1 Clinical data.</th>
<th>n = 59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46—97</td>
</tr>
<tr>
<td>Sex</td>
<td>24 women; 35 men</td>
</tr>
<tr>
<td>% stenosis</td>
<td>60—90</td>
</tr>
<tr>
<td>Side of the stenosis</td>
<td>29 right; 30 left</td>
</tr>
<tr>
<td>Cardiovascular risk</td>
<td>51</td>
</tr>
</tbody>
</table>

Inclusion criteria

Carotid artery stenosis, either symptomatic and >50% (NASCET), symptomatic and >70% (ECST), or asymptomatic. The degree of stenosis was measured using the Echo Doppler technique. Symptomatic stenosis was associated with strokes or transient ischemic attacks.

Exclusion criteria

A significant stenosis in another vascular territory, major illness such as cardiac, hepatic or renal failure, cancer of other relevant systemic disease, inability or refusal to undergo cerebral MRI.

Baseline clinical assessment

We assessed education, occupational status, job, marital status, living conditions, lifestyle habits (smoking, alcohol) and vascular risk factors. We also registered which drugs were currently being used.

All patients underwent a neurovascular imaging protocol in a 1.5-T clinical echo-planar unit (Philips Intera). A
whole brain diffusion MR (b values $0 - 1000 \text{s/mm}^2$; 5-mm slices covering the whole brain, TR 7000 TE 106 ms, $128 \times 128$ pixels, field of view 250 mm, one excitation) was acquired. ADC maps were automatically generated by the console software using a pixel-by-pixel approach. Furthermore, a T2-weighted scan (20 5-mm slices, TR 3374, TE 96 ms, two excitations, field of view 250 mm, matrix $512 \times 512$), coronal FLAIR scan (20 5-mm slices, TR 7000, TE 84 ms, one excitation, field of view 220 mm, matrix $256 \times 256$), and a 3dTOF MR Angiography were acquired.

Apparent diffusion coefficient measurements

After acquisition, data were transferred to an external workstation and loaded into OsiriX where regions of interest (ROI) were generated with an identical size of $0.35 \text{mm}^2$. Care was taken not to contaminate the area chosen with any kind of visible T2-weighted changes, tissue hyperintensity, leukoaraiosis or lesion (for symptomatic patients). Since hypoperfusion could be more present in the watershed regions, measurements in $10^{-3} \text{mm}^2/\text{s}$ were performed in the anterior and posterior paraventricular white matter (representing the carotid circulation) and in the thalamus and occipital regions, representing the posterior circulation (Fig. 1). This method of measurement reflects the maximum decrease in flow. For each region of interest, we performed the measurements contralateral and ipsilateral to the stenosis.

The data were analyzed by a research assistant who was blind to the patient’s clinical status and to the stenotic side.

Statistical analysis

Pair-wise comparisons between the stenotic side and the contralateral sides for each region of interest were conducted using a student $t$-test for dependent samples using Statistica 6.0 with a $P < 0.05$ considered significant. We further compared the stenotic and the contralateral sides in the symptomatic and the asymptomatic group also with a Student $t$-test.

Results

Overall, there was a significant increase in ADC values in the periventricular anterior (PVA) region on the stenotic side. The mean ADC value in PVA was $822.3 \pm 75.63 (10^{-3} \text{mm}^2/\text{s})$ on the ipsilateral side and $802.2 \pm 67.46$ on the contralateral side.

![Figure 2](image)

**Figure 2** Histogram: mean ADC in $10^{-3} \text{mm}^2/\text{s}$ of the different regions for all the patients ($n = 59$). PVA: periventricular anterior; PVP: periventricular posterior; THAL: thalamic; OCC: occipital.
side ($P = 0.0005$). In the periventricular posterior area (PVP), the difference between ipsilateral and contralateral sides was also significant. The mean ADC value was $819 \pm 71.55 (10^{-3}\text{mm}^2/\text{s})$ ipsilaterally and $800.1 \pm 65.2$ contralaterally ($P = 0.009$).

There was no significant difference between ipsilateral and contralateral sides for the thalamic area. The mean ADC value for this region was $765.9 \pm 60.2 (10^{-3}\text{mm}^2/\text{s})$ ipsilaterally and $772.3 \pm 58.17 (10^{-3}\text{mm}^2/\text{s})$ contralaterally ($P = 0.31$). Mean ADC values showed also no significant difference in occipital area: mean ADC on the ipsilateral side was $790.7 \pm 55.58 (10^{-3}\text{mm}^2/\text{s})$ and $786 \pm 55.21 (10^{-3}\text{mm}^2/\text{s})$ on the contralateral side ($P = 0.11$) (Fig. 2).

**Further analysis**

We also conducted these analyses separately for our symptomatic ($n = 33$) and asymptomatic ($n = 26$) patients.

The two groups did not differ in terms of the percentage of stenosis (mean for the asymptomatic group was $80 \pm 7.9%$ and $80 \pm 8.8$ for the symptomatic patients) (Table 2).

**Symptomatic patients**

Mean ADC values in the anterior paraventricular (PVA) region were significantly higher ipsilaterally than those contralaterally to the stenosis (respectively $824.17 \pm 77.74 (10^{-3}\text{mm}^2/\text{s})$ and $803.33 \pm 64.30 (10^{-3}\text{mm}^2/\text{s})$; $P = 0.0016$). Mean ADC values in the posterior paraventricular (PVP) region were also significantly higher on the ipsilateral than on the contralateral side (respectively $838.84 \pm 74.39 (10^{-3}\text{mm}^2/\text{s})$ and $810.33 \pm 67.14 (10^{-3}\text{mm}^2/\text{s})$; $P = 0.002$).

There was no difference between ipsilateral and contralateral ADC values in the thalamic region ($769.03 \pm 61.09$ for the ipsilateral side and $776.54 \pm 57.17 (10^{-3}\text{mm}^2/\text{s})$ for the contralateral side [$P = 0.31$]). For occipital regions, the mean ADC value was $793.91 \pm 60.63 (10^{-3}\text{mm}^2/\text{s})$ for the ipsilateral side and $787.85 \pm 61.96 (10^{-3}\text{mm}^2/\text{s})$ for the contralateral side of the stenosis. This difference was not significant ($P = 0.21$) (Fig. 3).

**Asymptomatic patients**

Mean ADC values in the PVA were significantly higher on the ipsilateral than on the contralateral side of the stenosis (respectively $826.98 \pm 72.61$ and $803.95 \pm 73.89 (10^{-3}\text{mm}^2/\text{s})$; $P = 0.018$). Mean ADC values in the PVP did not significantly differ between the two sides ($798.84 \pm 61.58$ ipsilaterally and $787.15 \pm 64.15$ contralaterally $[10^{-3}\text{mm}^2/\text{s}]$; $P = 0.34$).

Mean ADC values in the thalamic region did not differ significantly between the ipsilateral and contralateral side of the stenosis ($760.16 \pm 55.87$ for ipsilateral and $769.5 \pm 60$ for contralateral $[10^{-3}\text{mm}^2/\text{s}]; P = 0.39$) in the occipital region, the difference between the ipsilateral and contralateral side of the stenosis was also not significant ($785.66 \pm 47.37$ and $783.10 \pm 44.53$ respectively $[10^{-3}\text{mm}^2/\text{s}]; P = 0.42$) (Fig. 4).

**Correlation**

There was no correlation between age and mean ADC values in any region of interest, nor was there between percentage of stenosis and mean ADC values.

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**Table 2 Clinical data in the symptomatic and asymptomatic group.**

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic ($n = 33$)</th>
<th>Asymptomatic ($n = 26$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>33 (14 W; 19 M)</td>
<td>26 (10 W; 16 M)</td>
</tr>
<tr>
<td>Age</td>
<td>$75 \pm 13 \rightarrow$</td>
<td>$72.7 \pm 9.11$</td>
</tr>
<tr>
<td>$P$</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>% stenosis</td>
<td>$80 \pm 8.8 \rightarrow$</td>
<td>$80 \pm 7.9$</td>
</tr>
<tr>
<td>$P$</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Side of the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stenosis</td>
<td>17 right side,</td>
<td>12 right side;</td>
</tr>
<tr>
<td></td>
<td>16 left side</td>
<td>14 left side</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>risk (CV)</td>
<td>$\rightarrow$ 3 with 1 CV</td>
<td>$\rightarrow$ 9 with 1 CV</td>
</tr>
<tr>
<td></td>
<td>$\rightarrow$ 21 with 2 CV</td>
<td>$\rightarrow$ 12 with 2 CV</td>
</tr>
<tr>
<td></td>
<td>$\rightarrow$ 5 with 3 CV</td>
<td>$\rightarrow$ 1 with 3 CV</td>
</tr>
</tbody>
</table>
Discussion

In agreement with the literature [16], we found significantly higher ADC values on the ipsilateral side of a carotid stenosis, probably reflecting an impact of chronic hypoperfusion on the brain parenchyma in both symptomatic and asymptomatic patients. As previously discussed by Sionnes et al. [18], elevation of the ADC may be associated with vasogenic edema. In case of hypoperfusion induced by carotid stenosis, the expected hemodynamic change would be vessel dilatation and an increase in cerebral blood volume. An argument in favor of this hypothesis is that surgical removal of the stenosis results in a rapid decrease of the ADC values, to the same level as those of the contralateral hemisphere [16]. It would have been interesting to perform a perfusion analysis. However, this could not be done in our study, mainly because the patients received contrast for the MR angiography.

Sionnes et al. [16] argued that higher ADC values in the ipsilateral side of the stenosis were associated with leukoaraiotic development (preleukoaraiosis). While leukoaraiosis is classically associated with cardiovascular risk factors such as hypertension and hyperlipidemia, it is also associated slightly with carotid disease. O’Sullivan [19] found evidence that hypoperfusion plays a direct pathogenic role in the development of periventricular lesions in ischemic leukoaraiosis. They showed that cerebral blood flow was reduced in the periventricular white matter compared to in other brain regions (e.g. centrum semi-ovale). As leukoaraiosis corresponds to T2 changes [19–22], it will inevitably alter the ADC values, which is why we carefully chose to avoid including areas with any visible T2-weighted changes.

However, longitudinal follow-up data of ADC values and correlations with perfusion are still needed. It would also be interesting to study possible correlations between ADC values and neuropsychological test results of patients with carotid stenosis. Carotid endarterectomy or stenting is effective in stroke prevention in selected patients. The observed cognitive changes following this procedure have been debated [23]. Several studies showed improvements [24], others no change or even decline on postoperative neuropsychological tests [25]. Therefore, individuals with evidence of chronic hypoperfusion (increased ADC values) before intervention might be observed to show lower cognitive performance than patients without hypoperfusion.

Our data confirm that diffusion imaging and ADC values are an interesting and appropriate method to investigate patients with chronic hypoperfusion consecutive to carotid stenosis. It can improve our understanding of the mechanisms underlying alterations in brain structure that have not yet led to irreversible ischemia. Furthermore, this technique has the advantage that it is non-invasive and easy to conduct.

A limitation of our study was that it did not include a control group, and the patient sample was relatively small.

Conflicts of interest statement

None.

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References

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