Compromise of Brain Tissue Caused by Cortical Venous Reflux of Intracranial Dural Arteriovenous Fistulas
Assessment With Diffusion-Weighted Magnetic Resonance Imaging

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Background and Purpose—Cortical venous reflux (CVR) is a high risk factor for aggressive behavior of intracranial dural arteriovenous fistulas (DAVF). The pathological conditions in brain tissue affected by CVR were investigated by diffusion-weighted magnetic resonance imaging.

Methods—A retrospective review identified 56 patients with DAVFs who underwent diffusion-weighted imaging before treatment. Twenty patients had neurological symptoms corresponding to the brain area affected by CVR (Group I), 21 patients with CVR had no focal brain dysfunctions (Group II), and 15 patients had no CVR (Group III). Apparent diffusion coefficient (ADC) was measured for 11 brain areas predefined based on normal venous drainage patterns in the 56 patients and in 21 normal volunteers. The mean ADC ratio was calculated for each area by dividing the ADC value of patients by that of normal volunteers.

Results—Areas affected by CVR in Group I showed a mean ADC-to-control ratio of 0.72, which was significantly lower than that of Group II (0.96, P<0.01). Follow-up studies demonstrated significantly increased ADC ratios in brain areas affected by CVR after the DAVFs were treated successfully. The mean ADC ratio of an affected area remained low, with persistent symptoms in 1 patient who underwent palliative treatment.

Conclusions—Decreased ADC was observed in the brain parenchyma affected by CVR and was associated with regional brain dysfunction. Successful treatment of the DAVF increased the ADC toward normal levels. The ADC may be a useful indicator of the severity of CVR. (Stroke. 2011;42:1001-1006.)

Key Words: apparent diffusion coefficient, cortical venous drainage, cytotoxic edema, diffusion, dural arteriovenous fistula, MRI, venous edema

The classification of intracranial dural arteriovenous fistulas (DAVF) depends on the venous drainage pattern,1–3 which is generally accepted to be highly indicative of the risk for complications. DAVFs with cortical venous reflux (CVR), or retrograde leptomeningeal drainage (Borden Types 2 and 3, and Cognard Types IIb–V), represent aggressive lesions with annual risks for hemorrhage and nonhemorrhagic complications of 8.1 and 6.9%, respectively.4 However, the clinical features of CVR may not be uniform, and CVR with corresponding brain dysfunctions might carry several times higher risk for future hemorrhagic or nonhemorrhagic events than would CVR without such symptoms.5,6 However, the nature of such pathophysiological differences remains unclear.

Water mobility in the brain tissues under various conditions can be measured by the apparent diffusion coefficient (ADC), a quantitative parameter of diffusion-weighted magnetic resonance imaging (MRI).7 Low ADC values in ischemic lesions usually represent cytotoxic edema and indicate high risk of irreversible injury.8 High ADC values may be associated with hypertensive encephalopathy and are thought to indicate vasogenic edema, which is usually reversible.9 Previous studies on MRI findings of cerebral venous thrombosis have suggested that both vasogenic edema10,11 and cytotoxic edema11 may develop in the affected brain tissue. Experimental cerebral venous thrombosis in rats has suggested that the balance may depend on the severity as well as the duration of disturbed venous flow.12 Increased13,14 and decreased15 ADC values have also been observed in the brain parenchyma of patients with DAVF, but the pathological conditions caused by disturbed venous flow from CVR associated with DAVFs remain unclear.

The present study measured ADC values in the brain tissue affected by CVR to test the hypothesis that any changes in water diffusion might depend on the severity of CVR. The
mean ADC values of 11 areas of the brain, defined on the basis of anatomic venous drainage patterns, affected by CVR were compared with the ADC values of corresponding areas in normal volunteers.

Patients and Methods

Patient Characteristics

A retrospective review of 102 consecutive patients with intracranial DAVFs who were admitted to Kohnan Hospital between April 2003 and March 2010 identified 56 patients who fulfilled the entry criteria of MRI including diffusion-weighted imaging that was performed before treatment and did not show hemorrhagic findings. Twenty of these 56 patients presented with aggressive neurological symptoms including paresis, memory disturbance, aphasia, convulsion, drop attack, and ataxia. Thirty-one patients presented with nonaggressive symptoms including all ocular symptoms not related to intracranial hypertension, tinnitus, and isolated headache. Five patients were incidentally identified by neuroradiological investigations for unrelated reasons. All patients underwent conventional digital subtraction angiography of all cerebral and external carotid arteries before treatment. CVR was identified in 41 (73.2%) of the 56 patients with DAVFs. On the basis of the angiographic and clinical findings, the patients with DAVFs were divided into 3 groups: Group I (n=20), patients with CVR and aggressive symptoms corresponding to the affected brain regions; Group II (n=21), patients with CVR and no or nonaggressive symptoms; and Group III (n=15), patients without CVR.

Surgical Treatment

Surgical treatment was considered for all intracranial DAVFs except for asymptomatic Borden type 1. Intravascular embolization was first performed whenever possible to obliterate abnormal venous drainage and/or shunting points as far as possible. Patients with persistent CVR or significant shunt flow after embolization underwent open surgery to interrupt the CVR or to skeletonize affected sinuses. Embolization was performed with acrylic glue over 43 sessions in 22 patients and with platinum coils over 46 sessions in 36 patients. Ten patients underwent open surgery, including direct surgical interruption of the CVR in 7, and skeletonization of the affected sinuses in 3. Follow-up clinical and/or radiological findings were recorded 6 months after the last intervention in 17 of 20 patients in Group I, 17 of 21 patients in Group II, and 12 of 15 patients in Group III. Follow-up data were not available for 10 patients: 3 patients (2 in Group II and 1 in Group III) had undergone the last intervention within 6 months, and 7 patients (2 in Group II, 2 in Group III, and 3 in Group I) underwent radiosurgery before the follow-up study.

MRI Techniques

MRI techniques, including diffusion-weighted imaging, were described previously. Briefly, all MRI used a 1.5-T system (Signa imager, GE Medical Systems) with a standard head coil. Diffusion-weighted imaging used the single-shot, echo-planar spin-echo sequence with the following parameters: matrix size, 128×128; field of view, 22×22 cm; repetition time, 6000 ms; and echo time, 78 ms with b values of 0 and 1000 s/mm². Sixteen 6-mm-thick axial slices with an interslice gap of 2 mm, which included tissue from the entire brain, were imaged for 4 seconds in each of the 3 gradient directions. Isotropic images were constructed by averaging the 3 diffusion-weighted images. T2-weighted imaging used the fast spin-echo axial sequence with the following parameters: repetition time, 3000 s; echo time, 83 ms; matrix, 256×256; and field of view, 22×22 cm. Diffusion-weighted imaging sequence data were processed with Functool software (Advantage Workstation version 4.4, GE Medical Systems) to obtain the ADC values, which were calculated from diffusion trace images collected with b=0 and b=1000 on a pixel-by-pixel basis.

Areas of Brain Parenchyma and ADC Calculation

To investigate the impact of CVR on the brain parenchyma, region of interest (ROI) analysis of the ADC values was performed. The brain parenchyma was divided into 11 areas on the basis of normal venous drainage patterns (Figure 1). A total of 103 5-mm² ROIs were defined on the diffusion-weighted images of all 56 patients and 21 sex- and age-matched normal volunteers (http://stroke.ahajournal.org).
The ROIs in the gray and/or white matter were carefully selected to include only brain tissue, and to avoid areas affected by susceptibility artifacts and/or cerebrospinal fluid. Pixel-based ADC values of each ROI were averaged to give the mean ADC value of that ROI (mADC_{DAVF} in patients and mADC_{normal} in volunteers). This ADC value may vary between measurements, so the values could not be compared directly. Therefore, ADC values of the eyeballs and cerebrospinal fluid in the lateral ventricles were also measured (eyecsfADC_{DAVF} in patients and eyecsfADC_{normal} in volunteers). The ratio of mADC_{DAVF} to eyecsfADC_{DAVF}/mean eyecsfADC_{normal} was used to generate standardized ADC (sADC) values. The sADC ratio was calculated by dividing the sADC value of a patient by the mean ADC value of the same ROI of the normal volunteers to compensate for different ADC values in different brain areas, even in normal volunteers.20 Finally, the mean of all mean sADC ratios of ROIs in each brain compartment was defined as the sADC ratio of that compartment. These equations are given as follows:

\[
\text{sADC value} = \frac{\text{mADC}_{DAVF} \text{ value}}{(\text{eyecsfADC}_{DAVF}/\text{mean eyecsfADC}_{normal})}
\]

\[
\text{sADC ratio} = \frac{\text{sADC value}}{\text{mADC}_{normal} \text{ value}}
\]

**Statistical Analysis**

Statistical analyses were performed using GraphPad Prism (Version 5, GraphPad Software Inc.). Group comparison of categorical data used the \(\chi^2\) test. Numeric data are expressed as mean±SD, and comparisons between Groups I, II, and III were performed using Dunnett’s multiple comparison test if significant differences were found between the groups with 1-factor analysis of variance. Pre- and post-treatment comparison of sADC ratios was performed with the paired \(t\)-test. Differences were considered significant at a probability value of <0.05.

**Results**

Table 1 lists the baseline characteristics of our study population. The 3 groups showed no significant differences in age, but the male-to-female ratio of Group II was significantly lower than those of the other groups (\(P<0.05\)). The clinical features indicated some differences according to the location of the DAVFs, as no patient with cavernous sinus DAVF associated with CVR presented with aggressive symptoms, whereas 13 of the 20 patients with transverse-sigmoid sinus DAVF associated with CVR had aggressive symptoms corresponding to the affected brain areas.

### ADC Values in Normal Volunteers

The normal volunteer group consisted of 11 men and 10 women with mean age 62.3±10.9 years. The mean ADC values of all ROIs illustrated in Figure 1 are as follows: overall mean 0.755±0.067×10\(^{-3}\) mm\(^2\)/s; 0.702±0.054×10\(^{-3}\) mm\(^2\)/s in the anterior superior sagittal sinus area; 0.685±0.042×10\(^{-3}\) mm\(^2\)/s in the posterior superior sagittal sinus area; 0.752±0.056×10\(^{-3}\) mm\(^2\)/s in the sphenoid sinus area; 0.780±0.066×10\(^{-3}\) mm\(^2\)/s in the transverse sinus area; 0.791±0.038×10\(^{-3}\) mm\(^2\)/s in the petrosal vein area; and 0.784±0.060×10\(^{-3}\) mm\(^2\)/s in the straight sinus area.

### Pretreatment ADC Values

Patients in Group I showed aggressive symptoms corresponding to 33 areas receiving retrograde flow through CVR, and no or nonaggressive symptoms corresponding to 54 areas affected by CVR. Patients in Group II showed no or nonaggressive symptoms corresponding to 42 areas affected by CVR (Table 2). Diffusion-weighted imaging demonstrated high intensity in 19 of all 33 areas affected by CVR associated with aggressive symptoms and in 2 of all 96 areas affected by CVR associated with no or nonaggressive symptoms (\(P<0.01, \chi^2\) test). The mean sADC ratio of these affected areas was calculated for Groups I and II, and the mean sADC ratio was calculated of all areas for Group III (1.013±0.088). The mean sADC ratio in areas affected by CVR with aggressive symptoms in Group I (0.716±0.078) was significantly lower than that of areas affected by CVR with no or nonaggressive symptoms in Group II.
Changes in ADC Values After Treatment

Clinical symptoms improved after treatment in 16 of the 17 patients followed up by clinical and radiological examinations in Group I. Follow-up angiography revealed complete disappearance of the DAVF in 10 of these 16 patients. Small residual fistulae persisted, but no CVR was identified in the other 6 patients. Figure 3 compares the pre- and post-treatment sADC ratios. The mean sADC ratio of the areas affected by CVR was 0.749 ± 0.069 before treatment and 0.960 ± 0.072 6 months after treatment (P < 0.01, paired t-test) in the 16 patients (Figure 3A). Preoperatively, diffusion-weighted imaging showed high-intensity signals in the affected areas in 7 of these 16 patients, and T2-weighted imaging showed high-intensity signals in the same areas in 5 of these 7 patients. Follow-up T2-weighted imaging showed disappearance of the high-intensity signals in 1 patient, and partial resolution in 4 patients. Follow-up diffusion-weighted imaging detected no high-intensity signals in any patient. One patient in Group I with superior sagittal sinus DAVF underwent palliative treatment with a combination of intravascular and surgical procedures, but CVR persisted. The mean sADC ratio and high-intensity signals on diffusion-weighted imaging of the affected area did not significantly change (Figure 3A, arrows).

The mean sADC ratio of the affected area also significantly increased after treatment (P < 0.01, paired t-test) in 17 patients in Group II (Figure 3B). Initial and follow-up T2-weighted imaging detected no high-intensity signals. High-intensity lesions on initial diffusion-weighted imaging resolved completely after treatment in 2 patients.

Illustrative Case

An 82-year-old woman presented with Wernicke’s aphasia persisting for 12 hours and was admitted to our hospital. Left common carotid angiography showed a DAVF at the left transverse-sigmoid sinus fed by the occipital and ascending pharyngeal arteries (Figure 4A). The left sigmoid sinus-jugular bulb junction was occluded, so the DAVF drained retrogradely into the cortical vein of the left temporal lobe and into the right transverse sinus (Borden type 2; Figure 4B). Diffusion-weighted imaging demonstrated abnormal high intensity in the left temporal lobe with ADC reduction (Figure 4C, 4D). The patient underwent transvenous embolization for the involved sinus with detachable coils. The postoperative course was uneventful, and her symptoms improved dramatically. Follow-up angiography revealed no opacification of the DAVF. MRI performed 6 months after treatment showed disappearance of the abnormal lesion in the left temporal lobe. The mean sADC ratio of the affected area was 0.777 ± 0.107 before treatment and 0.915 ± 0.096 6 months after treatment. Please see the postoperative angiography and MRI of the illustrative case at http://stroke.ahajournals.org.

Discussion

This study indicated that ADC decreased significantly in the brain tissues affected by CVR, and was associated with

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**Table 2. Areas Affected by Cortical Venous Reflux of DAVFs**

<table>
<thead>
<tr>
<th>Affected Area</th>
<th>Group I (N=20)</th>
<th>Group II (N=21)</th>
<th>Total (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting Aggressive Symptoms</td>
<td>Presenting No or Non-Aggressive Symptoms</td>
<td>Presenting Aggressive Symptoms</td>
<td>Presenting No or Non-Aggressive Symptoms</td>
</tr>
<tr>
<td>Anterior SSS</td>
<td>6</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Posterior SSS</td>
<td>2</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Sphenoidal S</td>
<td>8</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Transverse S</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Petrosal V</td>
<td>2</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Straight S</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>54</td>
<td>0</td>
</tr>
</tbody>
</table>

SSS indicates superior sagittal sinus; S, sinus; V, vein.

(0.955 ± 0.067; **P** < 0.01, 1-factor analysis of variance followed by Dunnett’s multiple comparison; Figure 2). The mean sADC ratios showed no significant difference between areas affected by CVR in Group II and all areas in Group III.
corresponding aggressive symptoms. The ADC in these areas significantly improved after successful treatment, although recovery was not complete in most patients (Figure 3A). The ADC in areas affected by CVR associated with no or nonaggressive symptoms also significantly increased after treatment to near-normal levels, but with rather large variations (Figure 3B). Decreased ADC values mainly indicate cytotoxic edema caused by dysfunction of energy-dependent Na+/K+-ATPase in the cell membrane of acute ischemic lesions associated with arterial occlusion. Whether a similar mechanism is responsible for the present observation in DAVFs remains unclear. However, the measurement of ADC values may provide important information for assessing the severity of tissue injury in brain tissue affected by CVR in patients with DAVF.

The pathophysiological mechanisms that lead to venous infarction remain controversial. Conventional models hold that increased venous pressure impairs the uptake of extracellular tissue fluid into the capillary vessels and thus causes congestive edema.10 Alternatively, previous experimental studies showed that retrograde venous pressure might counteract capillary perfusion pressure to decrease cerebral blood flow, and thus cause arterial ischemia resulting in cellular or cytotoxic edema.12,21

Previous experimental and clinical diffusion-weight imaging studies of cerebral venous thrombosis have shown that ADC value was decreased,12,22,23 normal,23 increased,24 or heterogeneous.25,26 The ADC values decreased by 56% at 30 minutes after experimental cerebral venous thrombosis, and secondary increases in ADC subsequently developed in a rat model.12

Positron emission tomography showed evidence of hemodynamic impairment in the regions affected by CVR in 4 of 5 patients.27 These 4 patients presented with nonhemorrhagic neurological deficits, whereas the other patient with normal hemodynamics presented with only tinnitus. Positron emission tomography also showed abnormal cerebral blood flow and O2 extraction fraction in areas affected by CVR caused by DAVF, and these parameters improved significantly after definitive treatment.28 Another experimental report demonstrated a correlation between decreased ADC values and decreased cerebral metabolic rate of O2 and glucose.29 Two surgical patients with transverse-sigmoid DAVFs had selective neuronal damage in the cerebellum not evident on T2-weighted imaging, probably because of prolonged venous hypertension.30 These findings suggest that treatment may be recommended if the ADC value is significantly decreased, even if T2-weighted imaging detects no abnormal findings.

The limitations of this study include the small number of patients and retrospective approach. DAVF may involve the bilateral hemispheres to greater or lesser extents, and the pathophysiology is thought to be difficult to evaluate through absolute values of ADC or side-to-side comparison; therefore, we calculated the mean sADC ratio to compensate for...
intrinsic variation of ADC values at various sites in the brain and in individuals rather than comparing the ADC values of each area directly. Moreover, we excluded patients with DAVFs who presented with hemorrhage to avoid susceptibility artifacts. A prospective approach should be considered to clarify whether this method can identify patients who are prone to bleeding.

In conclusion, the present study indicated that ADC of brain tissue decreased with clinical severity of CVR caused by DAVF. Reduced ADC was mostly reversible with clinical improvement after effective treatment. The ADC may be a useful indicator of the severity of CVR, so a prospective study is needed.

Disclosures
None.

References
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Supplemental Figures and Figure Legend
Supplemental Figure 1

Illustrative presentation of compartmentalization of brain parenchyma according to normal venous drainage patterns and localization of ROIs for ADC analysis. A total of 103 ROIs (white circles, 5 mm² each) were placed within the parenchyma avoiding inclusion of sulci. A mean of pixel-based ADC values in a ROI served as a mean ADC value of the ROI. Standardized ADC ratios (sADC ratio) for each compartment were calculated as described in the text. Abbreviations: SSS, superior sagittal sinus; S, sinus; V, vein.
Supplemental Figure 2

(A, B) Postoperative left common carotid angiograms obtained 6 months after transvenous embolization demonstrating complete disappearance of the dural arteriovenous fistula and cortical venous reflux, and the improved parenchymal circulation (arrows). Diffusion-weighted image (C) showing the disappearance of the abnormal high intensity lesion, and ADC map (D) showing the ADC reduction was nearly resolved after treatment. White circles in D indicate ROIs (5mm² each) placed on the affected areas for ROI analyses.