Impairment of Cerebral Perfusion and Infarct Patterns Attributable to Vasospasm After Aneurysmal Subarachnoid Hemorrhage

A Prospective MRI and DSA Study

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Background and Purpose—The objective of this study was to investigate disturbance of perfusion and infarct patterns attributable to cerebral vasospasm (CVS) after subarachnoid hemorrhage (SAH).

Methods—One hundred seventeen patients with aneurysmal SAH specifically selected at high risk for CVS were enrolled in this prospective study. One hundred twelve patients underwent surgical (n=63) or endovascular (n=59) therapy. For assessment of CVS, relative diameter changes of proximal and distal vessel segments on follow-up angiography at day 7 ± 3 after SAH were analyzed in relation to baseline measurements, and cerebral circulation times were measured. Postprocedure MRI was undertaken selectively at four time points: within 3 days, between days 4 and 6, day 7 to 14, and day 15 to 28 from onset of SAH, including perfusion- and diffusion-weighted images. Procedure-related lesions were excluded and CVS-associated infarct patterns analyzed.

Results—Occurrence of angiographic CVS was as high as 87.5% between days 7 and 14 and 52.5% showed new infarcts. Eighty-one percent of the infarcts were related to severe CVS (vascular narrowing >66%) and significant (P<0.001) cerebral circulation times prolongation of 8.47 ± 2.25 seconds (time-to-peak delay on perfusion-weighted image: 6.52 ± 4.75 seconds), 16% were associated with moderate CVS (34% to 66% vascular narrowing; cerebral circulation times prolongation: 4.72 ± 0.66 seconds). Besides territorial (47%), lacunar (20%), and watershed infarcts (26%), in 7%, band-like cortical lesions developed without evidence for severe CVS.

Conclusions—CVS after SAH may involve the complete arterial system from the circle of Willis up to the distal vessel segments. Depending on the variable types of collateral flow, location of affected vessels segments as well as the degree of CVS may induce different infarct patterns. (Stroke. 2007;38:1831-1836.)

Key Words: angiography ■ MRI ■ SAH ■ stroke ■ vasospasm

Despite extensive experimental and clinical research, arterial cerebral vasospasm (CVS) remains one of the main causes for poor clinical outcome in patients after aneurysmal subarachnoid hemorrhage (SAH).1 Vascular narrowing of proximal or distal arterial segments occurs in up to 70% to 95% on digital subtraction angiography (DSA) when performed 7 to 14 days after aneurysm rupture.2 Delayed ischemic neurological deficits and infarcts on CT caused by CVS, ie, symptomatic vasospasm, range between 20% and 40%.1,3–5 Moreover, when using diffusion-weighted MRI as a highly sensitive method also for detecting small ischemic lesions,6 CVS-related infarcts could be detected in up to 81%.4

However, the disturbance of cerebral perfusion after SAH is not only caused by proximal artery segment vasospasm, but also by distal arterial vasospasm as well as the intraparenchymal arterioles,7–9 resulting in prolonged cerebral circulation times (CCT) on DSA.10 Furthermore, additional factors such as cerebral edema, hydrocephalus, and secondary intraparenchymal hemorrhage may induce increased intracranial pressure with consecutive prolonged CCT.11 A review of the literature yielded only a few MRI studies12–16 with a limited number of patients and only retrospective assessment of cerebral perfusion disorders and infarct development caused by CVS.

The aim of this prospective study was to analyze perfusion disturbances and infarct patterns in patients with CVS with sequential diffusion- and perfusion-weighted MRI with reference to additional DSA.

Patients and Methods

Study Population and Study Design

Between January 2002 and August 2006, 117 patients specifically selected at high risk for CVS attributable to subarachnoid clot
volume (grade 3 according to the Fisher classification) out of 364 patients admitted to the department of neurosurgery with aneurysmal SAH of all clinical grades were enrolled in a prospective serial MRI and DSA study. Inclusion criteria were (1) angiographically confirmed saccular aneurysm, (2) clinically high risk for the development of CVS, and (3) onset of SAH within 48 hours before admission. Exclusion criteria were (1) contraindications for MRI, eg, pacemakers or magnetic implants, (2) SAH attributable to another cause, (3) severe concomitant disease, (4) established large cerebral infarcts, (5) large intracerebral hemorrhage, (6) medically refractory intracranial pressure greater than 25 mm Hg, (7) tentorial herniation, (8) recurrence of warning hemorrhage, and (9) small amount of subarachnoid clot volume.

After aneurysm occlusion, MRI was performed selectively at four time points: within 3 days (n=52), between days 4 and 6 (n=56), day 7 to 14 (n=80), and day 15 to 28 (n=36) after SAH. For the first time point, 60 patients received CT instead of MRI within 48 hours after surgical (63 patients) or endovascular (59 patients) therapy to identify procedure-related lesions. Forty-six patients had MRI at one time point, 41 patients had MRI at 2 time points, and in 24 patients, MRI was performed at 3 time points and 6 patients received MRI at 4 time points.

Attributable to poor clinical status, 5 moribund patients were not treated. All patients underwent biplane DSA before surgery or coil embolization in the first 48 hours and at day 7 to 14 after SAH. Patients received MRI and subsequent DSA ahead of schedule when one of the following signs were found: (1) newly developed neurological deficit, (2) a decrease of at least 2 points on the Glasgow Coma Scale in the absence of other identifiable structural or clinical causes, or (3) an increase of greater than 150 cm/s in transcranial Doppler mean arterial flow velocity. The study was approved by the local ethical committee.

**Patient Management**

After admission, hypovolemia, hyponatremia, and hypotension were treated irrespective of the unsecured aneurysm. Target values included a cerebral perfusion pressure greater than 60 mm Hg, a central venous pressure greater than 10 mm Hg, and hematocrit less than 0.45. A ventricular drain was placed in patients with Hunt and Hess grades 4 and 5 and in those with hydrocephalus and Hunt and Hess grade 3. Selection of patients for surgery or endovascular treatment was accomplished by an interdisciplinary team. We followed an early surgery strategy (24 to 48 hours) in patients of all clinical grades unless the patients were hemodynamically unstable or moribund. Surgery was routinely performed in a hypothermic patient (32°C to 33°C), whereas coil embolization was performed in a normothermic patient. After aneurysm obliteration, all patients were treated in the neurosurgical intensive care unit. Again, great care was taken to compensate for increased diuresis and natriuresis and to maintain a normovolemic and normotensive state. Total daily fluid turnover at this stage of treatment ranged from 4 to 6 L in most patients. All patients received nimodipine from the day of admission. Fludrocortisone was administered as an adjunct in case of hyponatremia, and desmopressin was used to control excessive diuresis. Routine surveillance included daily transcranial Doppler measurements and, in selected cases, multimodal monitoring of brain tissue O2, regional cerebral blood flow (thermodilution microprobe), and interstitial metabolites (microdialysis). In cases of symptomatic vasospasm, hypervolemia was instituted and hypertension was induced with catecholamines following a stepwise protocol. When hypertension–hypervolemia–hemodilution therapy failed, patients with perfusion-weighted image/diffusion-weighted image (DWI/DWI) mismatch on MRI ("tissue at risk") attributable to proximal vasospasm were selected for angioplasty.

**MRI Protocol**

MR examinations were performed at 1.5 T (Magnetom Vision; Siemens). The standardized imaging protocol included native axial T2-weighted images (T2 WI), axial T2*WI, and axial fluid-attenuated inversion-recovery sequences. In addition, all patients received biplane DWI and PWI. DWI was performed with a single-shot echoplanar imaging spin echo sequence (TE=123 ms, field of view=230×230 mm, matrix 128×128 pixel, 19 slices, slice thickness=6 mm, b=1000 s/mm²). Acquisition of bolus tracking PWI was performed with a gradient-echo echoplanar imaging sequence (TE=60.7 ms, field of view=230×230 mm, matrix=128×128 pixel, slice thickness=5 mm). After standardized intravenous contrast agent injection (0.1 mmol/kg Gd-DTPA) with a flow rate of 5 mL/s, 40 T2* WI for each of the 12 slices at intervals of 2 seconds were obtained. In all major vessel territories as well as in adjacent areas of restricted diffusion on DWI and reduced apparent diffusion coefficient, regions were measured for time-to-peak (TTP) values and mean-transit-time values.

**Digital Subtraction Angiography**

Evaluation of selective DSA included (1) proximal and (2) distal CV angiography as well as (3) CCT of injected contrast medium bolus.

For the assessment of proximal CVS, the diameter of the proximal segments of the middle cerebral artery (M1 segment), anterior cerebral artery (ACA, A1 segment), posterior cerebral artery (P1 segment), the distal part of the internal carotid artery (C1 segment), as well as the intradural vertebral artery (V4 segment) and the basilar artery were measured in absolute values and set in relationship to the average diameter of the middle cerebral artery (M1 segment), anterior cerebral artery (A2, ie, A2–A5 segments; ascending part [A2], precallosal part [A3], and intracallosal parts [A4 and A5]), the middle cerebral artery (M2, ie, M2–M4 segments; insular segment [M2], opercular segment [M3], and terminal segment [M4]) and the posterior cerebral artery (P2, ie, P2–P3 segments; circular segment [P2] and cortical segment [P3]) were analyzed using a qualitative grading scale (no vascular narrowing, mild, moderate, and severe vascular narrowing). In addition, focal or diffuse vessel involvement was assessed.

CCT at DSA was defined by the time period between intradural arterial inflow of the contrast medium bolus at the level of the carotid siphon and the contrast enhancement of the bridging veins. Three to 6 frames per second were acquired in the first 10 seconds after contrast medium injection.
Vasospastic infarction was defined by new ischemic lesions on DWI and concomitant vascular narrowing on DSA. Procedure-related infarcts detected on CT or MRI within 24 to 48 hours postprocedure were excluded.

Data Analysis
Measurement of vessel diameters and the calculation of relative diameter changes on follow-up DSA as well as CCT and TTP evaluation were performed blindly and independently by 2 experienced investigators (S.W., H.L.). Neuroradiological values were expressed as mean ± SD. Correlation between angiographic diameter of the arteries and the CCT and the TTP delay was analyzed by Pearson’s correlation coefficient (r). A probability value <0.05 was considered significant.

Results
A total of 117 patients (68 females, 49 males, age 30 to 88 years, mean: 52.1 ± 11.8 years) with aneurysmal SAH (grade 1 according to the Hunt and Hess classification: 14 patients; grade 2: 47 patients; grade 3: 32 patients; grade 4: 16 patients; grade 5: 8 patients) were included in the study. Figure 1 illustrates the time course of occurrence of CVS in the first 28 days after SAH. Between days 4 and 6, frequency was 45.2% (CVS with DWI lesions: 19.4%) and as high as 87.5% (CVS with DWI lesions: 52.5%) when MRI and DSA were performed between day 7 and day 14. CCT and perfusion deficits on PWI, ie, TTP delay, are summarized in Table 1. Severe vasospasm resulted in extension of CCT up to 8.47 seconds (SD ± 2.25 seconds) and was more as double so long as compared with patients without CVS (3.74 seconds; SD ± 0.34 seconds). TTP delay in the affected arterial territories was more distinct in all 3 categories of CVS, especially when severe vasospasm was present (6.52 seconds; SD ± 4.75 seconds).

The patterns of ischemic brain lesions attributable to CVS were differentiated in (1) watershed infarcts (hemodynamic infarcts); (2) large infarcts in the territories supplied by the ACA, middle cerebral artery, or posterior cerebral artery involving cortical and adjacent subcortical structures, ie, territory infarcts; (3) lacunar infarcts in the basal ganglia, thalamus, and white matter (Figure 2); and (4) focal band-like laminar cortical lesions (Figure 3).

Eighty-one percent of the infarcts were associated with severe CVS, whereas 16% occurred when moderate CVS was present; and in 3%, DSA revealed none or only mild vascular narrowing. Thirty-five of 48 patients had multiple infarctions (one infarct: 13 patients; 2 infarcts: 7 patients; 3 infarcts: 13 patients; 4 infarcts: 8 patients; 5 infarcts: 6 patients; 6 infarcts: one patient). In total, 134 CVS-related ischemic lesions occurred on DWI and T2WI. Table 2 summarizes frequency of infarct patterns and time period of development. Angiographic extend of vasospasm and associated infarct

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**TABLE 1. Cerebral Circulation Time and Perfusion Deficits in Relationship to Severity of Vasospasm**

<table>
<thead>
<tr>
<th>Vasospasm</th>
<th>CCT t (sec)</th>
<th>DSA t (sec)</th>
<th>MRI/PWI t (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3.74 (SD ± 0.34)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mild</td>
<td>4.11 (SD ± 0.92)</td>
<td>0.98 (SD ± 0.44)</td>
<td>...</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.72 (SD ± 0.66)*</td>
<td>1.26 (SD ± 1.43)</td>
<td>...</td>
</tr>
<tr>
<td>Severe</td>
<td>8.47 (SD ± 2.25)*</td>
<td>6.52 (SD ± 4.75)*</td>
<td>...</td>
</tr>
</tbody>
</table>

*P < 0.01 and †P < 0.001 versus no CVS.

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Figure 2. Lacunar infarct in the basal ganglia. A, Baseline angiogram shows saccular aneurysm in the middle cerebral artery bifurcation (arrow, oblique projection). B, Day 7 angiogram reveals focal CVS (arrow) of the right A1 segment. C, Day 7 DWI shows new infarction in the territory of the central anteromedial arteries originating from the proximal A1 segment. D, PWI disclosed no additional perfusion deficit.
patterns are listed in Table 3. DSA disclosed CVS in 87 patients. In 60 patients, proximal as well as distal CVS was present; 23 patients had proximal vasospasm and in 4 patients (3 patients with anterior communicating artery aneurysms, one patient with pericallosal artery aneurysm), DSA showed only distal CVS at the A2–A5 segments.

**Discussion**

In accordance with other investigations, occurrence of CVS amounted to 87.5% in the second week after aneurysmal SAH, reflecting the time course in development of CVS. However, despite DWI, which is a sensitive MRI method reflecting cytotoxic edema with restricted diffusion in acute ischemic lesions, the rate of vasospastic infarcts was 52.5% and not as high as the infarct rate of 81% reported by Kivisaari et al, who studied long-term follow up after SAH with conventional MRI sequences without DWI. One reason, therefore, might be the inclusion of infarcts caused by other etiologies, eg, procedure-related. Regarding the possible difficulty of recognizing neurological worsening in patients with impaired consciousness or coma, one advantage of the presented study is the assessment of vasospastic infarcts using DWI. However, ischemic-related neurological worsening without infarct evolution is reported, reflecting reduced cerebral perfusion with impaired functional but sufficient structural metabolism.

In line with the results reported by Okada et al, CCT in patients without CVS was prolonged at 0.44 (SD ±0.34 seconds) as compared with healthy volunteers. Reasons therefore might be a raised intracranial pressure in patients with acute SAH attributable to hydrocephalus, diffuse brain edema, or additional intraparenchymal hemorrhage. Regarding a modern DSA unit with an image resolution of 1024×1024 pixel, classification of CVS in the presented study allowed 4 categories, ie, none, mild, moderate, or severe vascular narrowing to be determined unlike the assessment of Kassell et al, who defined severe vasospasm when vascular narrowing was more than 50%.

Attributable to the exponential correlation, increasing vasocostriction resulted in an impressive prolongation of CCT up to 4.73 seconds (SD ±2.25 seconds) when severe vasospasm was present. Moreover, by using PWI, TTP delay was pronounced (6.52 seconds, SD ±4.75 seconds). The time differences measured on DSA and MRI might be attributable to the fact that PWI allows also the assessment of small regions of interest, especially in watershed regions reflecting more severe impairment of cerebral perfusion, whereas on DSA, the filling of the bridging veins often reflects greater territories attributable to the convergence of venous drainage.

Analysis of cerebral perfusion (Table 1) and infarct evolution (Table 3) suggested that the perfusion delay was smaller than in patients with infarcts by arteriosclerosis or embolic disorders. On one hand, this difference might reflect a lower tolerance to ischemia of the cerebral parenchyma after SAH. On the other hand, CVS is a very dynamic process that fluctuates over time and perfusion studies, like snapshots, are therefore not always representative of maximal hypoperfusion, whereas thromboembolic ischemia is more uniphasic and acute perfusion scans are thus more reliable markers for maximal hypoperfusion. In addition, TTP and mean-transit-time maps measured with the bolus tracking method have pitfalls. Especially when diffuse CVS affects both hemispheres, the comparison of different vascular territories is impaired. Limitations of CCT measurements on DSA could be a low number of frames per second, eg, one image per second.

In previous MRI and CT studies assessing CVS-induced infarct pattern, only Shimoda et al discriminated cortical ischemic lesions and perforator-associated infarcts in the basal ganglia, thalamus, and corona radiata. Single or multiple cortical lesions occur in 85% in patients with symptomatic CVS reflecting the most frequently specimen in major vessel CVS. However, in 75%, lesions were also detected referable to intraparenchymal vessels. In a recent CT-based analysis, 39% of the patients had infarcts attributable to CVS. Sixty-one percent of these infarcts were located corti-

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**TABLE 2. Frequency and Patterns of CVS-Related Infarcts (symptomatic CVS)**

<table>
<thead>
<tr>
<th>Days After SAH</th>
<th>Watershed</th>
<th>Territorial*</th>
<th>Lacunar</th>
<th>Laminar</th>
<th>Cortical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–6</td>
<td>10</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>7–14</td>
<td>14</td>
<td>34</td>
<td>12</td>
<td>4</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>15–28</td>
<td>…</td>
<td>12</td>
<td>…</td>
<td>…</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>70</td>
<td>24</td>
<td>16</td>
<td>134</td>
<td></td>
</tr>
</tbody>
</table>

*ACA, middle cerebral artery, posterior cerebral artery.

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Figure 3. Focal band-like cortical lesion. A, Day 5 CT shows sulcal clots and adjacent hypodense cortex (arrows). B, MRI (T2WI) at day 6 reveals a hyperdense band-like cortical lesion. C, DSA (day 6) exhibits only mild proximal and distal CVS.
cally, 18% in the deep white matter and the basal ganglia, and 21% cortically as well as in the deep brain structures. Different pathophysiological mechanisms and different degrees of severity of the same vascular process were assumed. An advantage of the presented study is the analysis of infarct pattern on DWI in regard to the DSA findings. Watershed infarcts were solely associated with severe CVS. In addition, territorial type and perforator type of infarcts mostly occur when severe CVS was present but were also detected in patients with moderate vasospasm.

As a result of a venturi-like effect leading to flow separation in poststenotic vessel segments, the orifices of perforating arteries are affected (Figure 2B).26 Therefore, circumscribed ischemia in deep-sited areas of the brain supplied by perforating arteries originating from the proximal vessel segments may be a likely consequence of the pressure collapse at the perforator orifices. In contrast, in 7 (44%) of the 16 focal band-like infarcts with adjacent thick sulcal clots, DSA showed none or only mild CVS suggesting a different underlying physiopathological mechanism. This might be related to local disturbances of cortical microvascularization attributable to vasoconstriction of small arteries and arterioles7 that cannot be detected by angiography or transcranial Doppler sonography, irrespective of possible local toxic effects of sulcal clots. However, an infarct in a cortical or subcortical location is itself not proof positive that the most distal segments were vasospastic, because of course proximal CVS combined with variable types of distal collateral flow could lead to similar infarct patterns.27 Moreover, it has been suggested that small focal cortical infarcts may result from cortical spreading ischemia with neuronal depolarization waves triggering episodes of acute severe vasoconstriction.20 Furthermore, the band-like lesion pattern in our study was different from that caused by hypoxia or severe increased intracranial pressure with diffuse cortical hyperperfusion.21

Especially small lesions in the midline structures, in the deep white matter and also circumscribed in the cortex, are detected better on DWI as compared with CT.6 However, even if the lesions are small in size, strategic localization may cause remarkable clinical symptoms. Besides motor system dysfunction when the corticospinal tract is involved, infarcts located in the inferior medial thalamus supplied through posterior thalamoperforating arteries28 and infarcts of the anterior lateral thalamus supplied by the tuberohalamic artery28 are associated with distinct neuropsychological disorders,29 potentially causing broad disability in the outcome of patients after successful treatment of aneurysm. In addition, infarcts of midline structures such as fornices and corpus callosum may lead to cognitive and behavioral impairment.30

In conclusion, CVS after SAH may involve the complete arterial system from the circle of Willis up to the distal vessel segments. Depending on the variable types of collateral flow, the location of affected vessel segments and the degree of vascular narrowing may induce different infarct patterns, including also small lesions well detected on DWI.

### Disclosures

None.

### References


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