Impairment of Cerebral Perfusion and Infarct Patterns Attributable to Vasospasm After Aneurysmal Subarachnoid Hemorrhage
A Prospective MRI and DSA Study

Stefan Weidauer, MD; Heinrich Lanfermann, MD; Andreas Raabe, MD; Friedhelm Zanella, MD; Volker Seifert, MD; Jürgen Beck, MD

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;38:000-000.)

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). 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. Delayed ischemic neurological deficits and infarcts on CT caused by CVS, ie, symptomatic vasospasm, range between 20% and 40%. Moreover, when using diffusion-weighted MRI as a highly sensitive method also for detecting small ischemic lesions, 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, resulting in prolonged cerebral circulation times (CCT) on DSA. Furthermore, additional factors such as cerebral edema, hydrocephalus, and secondary intraparenchymal hemorrhage may induce increased intracranial pressure with consecutive prolonged CCT. A review of the literature yielded only a few MRI studies 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...
Occurrence of CVS after SAH

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Day 4 - 6</th>
<th>Day 7 - 14</th>
<th>Day 15 - 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>no CVS</td>
<td>54.8</td>
<td>35</td>
<td>20.3</td>
</tr>
<tr>
<td>ang. CVS without DWI lesion</td>
<td>25.8</td>
<td>52.5</td>
<td>52.6</td>
</tr>
<tr>
<td>ang. CVS with DWI lesion</td>
<td>19.4</td>
<td>21.1</td>
<td>21.1</td>
</tr>
</tbody>
</table>

Figure 1. Occurrence and time course of CVS in 117 patients. CVS was classified into angiographic vasospasm on DSA with concomitant DWI lesions on MRI and vascular narrowing without DWI lesions.

Digital Subtraction Angiography

Evaluation of selective DSA included (1) proximal and (2) distal CVS 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 absolute values of the extradural petrous segment of the internal carotid artery11 or the extradural vertebral artery (V3 segment), respectively, on anterior–posterior projections and lateral projections (internal carotid artery, vertebral artery, basilar artery). These ratios of baseline and follow-up DSA were compared and relative diameter changes on the follow-up angiograms were expressed in relation to the initial baseline measurement (%).2,5,17 Presence of CVS was classified in none (0% to 10%), mild (11% to 33%), moderate (34% to 66%), or severe (67% to 100%) vascular narrowing, and focal (<50% of the segment length) or diffuse (>50% of the segment length) involvement in at least one vessel segment.

Changes in the diameter of distal vessel segments of the ACA (A2+, ie, A2–A5 segments; ascending part [A2], precallosal part [A3], and callosomarginal segments [A1]; 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 score (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.14,18 Three to 6 frames per second were acquired in the first 10 seconds after contrast medium injection.

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.
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 blinded 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)19; (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).20,21

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

---

**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 (TTP delay) 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>1.26 (SD ± 1.43)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.72 (SD ± 0.66)*</td>
<td>6.52 (SD ± 4.75)*</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.
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,1,3,4,16 occurrence of CVS amounted to 87.5% in the second week after aneurysmal SAH, reflecting the time course in development of CVS.2 However, despite DWI, which is a sensitive MRI method reflecting cytotoxic edema with restricted diffusion in acute ischemic lesions,6 the rate of vasospastic infarcts was 52.5% and not as high as the infarct rate of 81% reported by Kivisaari et al,4 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.12 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,22 reflecting reduced cerebral perfusion with impaired functional but sufficient structural metabolism.23

In line with the results reported by Okada et al,11 CCT in patients without CVS was prolonged at 0.44 (SD±0.34 seconds) as compared with healthy volunteers.18 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,10 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,5 who defined severe vasospasm when vascular narrowing was more than 50%.

Attributable to the exponential correlation, increasing vasoconstriction resulted in an impressive prolongation of CCT up to 4.73 seconds (SD±2.25 seconds) when severe vasospasm was present.10,24 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.11

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.23 On one hand, this difference might reflect a lower tolerance to ischemia of the cerebral parenchyma after SAH.24,25 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.23,24 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.23 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 al16 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,3 39% of the patients had infarcts attributable to CVS. Sixty-one percent of these infarcts were located corti-

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

<table>
<thead>
<tr>
<th>Infarct Pattern</th>
<th>Days After SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watershed</td>
<td>Territorial*</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>4–6</td>
<td>10</td>
</tr>
<tr>
<td>7–14</td>
<td>14</td>
</tr>
<tr>
<td>15–28</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
</tr>
</tbody>
</table>

*ACA, middle cerebral artery, posterior cerebral artery.
could lead to similar infarct patterns. 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 vasocostriction. 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.

Especially small lesions in the midline structures, 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). 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 apertures. 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 pathophysiological mechanism. This might be related to local disturbances of cortical microvascularization attributable to vasocostriction of small arteries and arterioles 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 collateral flow could lead to similar infarct patterns. 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 vasocostriction. 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.

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. 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 arteries and infarcts of the anterior lateral thalamus supplied by the tuberothalamic artery are associated with distinct neuropsychological disorders, 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.

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.

**Table 3. Infarct Patterns in Relationship to Severity and Location of Vasospasm**

<table>
<thead>
<tr>
<th>Infarct Pattern (%)</th>
<th>Mild No</th>
<th>Proximal</th>
<th>Distal</th>
<th>Moderate No</th>
<th>Proximal</th>
<th>Distal</th>
<th>Severe No</th>
<th>Proximal</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watershed (26%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>28</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Territorial (47%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>11</td>
<td>4</td>
<td>45</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar (20%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>6</td>
<td>2</td>
<td>17</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laminar cortical (7%)</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>2%</td>
<td>16%</td>
<td>81%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total number of CVS-related infarcts amounts to 134 (see Table 2). If proximal CVS (C1, M1, A1, P1, V4, basilar artery) as well as distal CVS (M2+, A2+, P2+) were present, the infarcts (n=68) are listed twice.

**References**

Impairment of Cerebral Perfusion and Infarct Patterns Attributable to Vasospasm After Aneurysmal Subarachnoid Hemorrhage. A Prospective MRI and DSA Study
Stefan Weidauer, Heinrich Lanfermann, Andreas Raabe, Friedhelm Zanella, Volker Seifert and Jürgen Beck

Stroke. published online April 19, 2007;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2007/04/19/STROKEAHA.106.477976.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/