Time course of blood velocity changes related to vasospasm in the circle of Willis measured by transcranial Doppler ultrasound

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Fifty patients with ruptured aneurysms were operated on within 72 hours after the first subarachnoid hemorrhage (SAH). To prevent symptomatic vasospasm, the patients were given the calcium channel blocker, nimodipine, intravenously (2 mg/hr) for 14 days and orally (60 mg four times daily) for another 7 days. At short intervals (at least every 3rd day) the blood flow velocity in the different segments of the circle of Willis was measured with a noninvasive transcranial Doppler ultrasonography method. Within the first 72 hours after SAH, the velocity was normal in the large branches of the circle of Willis and angiography revealed no signs of vasospasm. The Doppler frequency changes that relate to blood flow accelerated between Days 3 and 10, and maximum blood flow velocities were recorded between Days 11 and 20, with normalization occurring within the following 4 weeks. The changes showed a significant relationship to the source of SAH, the side of the operative approach, and the method of nimodipine administration. A comparison between the angiographically proven diameter of spastic arteries and the Doppler-measured blood flow velocity showed an inverse relationship in flow of the middle cerebral artery and the internal carotid artery that was statistically highly significant (p < 0.001) while this correlation was only slightly significant in the A1 segment of the anterior cerebral artery (p = 0.054). Seven patients (14%) developed delayed ischemic deficits (DID's), which were all functionally reversible. One patient (2%) died as a result of decompensated vasospasm. Based on the information provided by Doppler measurement of the individual blood flow velocity changes due to vasospasm, preventive hypertensive treatment was introduced to improve the perfusion pressure while patients were still in an asymptomatic stage. Among the last 40 patients who were treated according to this regimen, reversible DID's were observed in only three patients (7.5%) and postoperative angiography to detect vasospasm was not necessary.

KEY WORDS • ultrasonography • subarachnoid hemorrhage • nimodipine • vasospasm • aneurysm

THE surgical treatment of ruptured cerebral aneurysms has been made safer by the use of microsurgical techniques. Nevertheless, postoperative vasospasm remains a major complication associated even with early aneurysm surgery, producing delayed ischemic deficits (DID's) in 2% to 20% of all cases. Until now, the only way to establish the time course of vasospasm has been by angiography. However, performing angiography on patients with vasospasm poses an even greater risk of neurological deficits. Noninvasive cerebral blood flow (CBF) measurements can detect a reduction of blood flow following subarachnoid hemorrhage (SAH) as an effect of vasospasm, but cannot prove narrowing of the lumen itself. Transcranial Doppler ultrasonography now makes it possible to measure, atraumatically and repeatedly, the changes in blood flow velocity that occur with vasospasm. About 6000 individual velocity measurements were carried out on the circle of Willis in 50 consecutive patients who underwent early operation for ruptured aneurysms. On the basis of these measurements, the following problems were studied: the time course of vasospasm in individual arteries after SAH; the relationship of the time course to the origin of the hemorrhage; the effect of washing out clots from the subarachnoid space; the efficacy of prophylactic therapy with the calcium channel blocker nimodipine; and the value
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### TABLE 1

<table>
<thead>
<tr>
<th>Arterial Location of Aneurysm</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>anterior communicating</td>
<td>23</td>
</tr>
<tr>
<td>posterior communicating</td>
<td>4</td>
</tr>
<tr>
<td>middle cerebral</td>
<td>13</td>
</tr>
<tr>
<td>anterior cerebral (A1 segment)</td>
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</tr>
<tr>
<td>anterior choroidal</td>
<td>2</td>
</tr>
<tr>
<td>interior carotid (bifurcation)</td>
<td>3</td>
</tr>
<tr>
<td>multiple locations</td>
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<tr>
<td>posterior inferior cerebellar</td>
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</tr>
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</table>

### TABLE 2

<table>
<thead>
<tr>
<th>SAH Grade*</th>
<th>Extent of SAH on Preoperative Computerized Tomography</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I thin localized layer</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>II thick layer in 2 of the 3 subarachnoid compartments (basal cisterns, sylvian fissures, interhemispheric space), or in 1 subarachnoid compartment &amp; at cortical surface</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>III severe diffuse SAH with thick layers in all 3 subarachnoid compartments, or in 2 &amp; at cortical surface</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

* Grade according to Fisher, et al.*

### Clinical Material and Methods

The series included 50 consecutive patients (27 women and 23 men) who were operated on within 72 hours after a single SAH that had been confirmed by lumbar puncture, or computerized tomography (CT), or both. In this group, 68% were operated on within 24 hours after the SAH, 24% between 25 and 48 hours, and 8% between 49 and 72 hours. The locations of the aneurysms are listed in Table 1, and CT grading of the SAH according to the modified method of Fisher, et al., is presented in Table 2. The relationship of the preoperative neurological clinical grade according to Hunt and Hess to the severity of the SAH is shown in Table 3.

Transcranial Doppler ultrasound recordings* were performed in each patient at least every 3rd day during the post-SAHI period. Blood flow velocities were measured in the middle cerebral artery (MCA), the supraclinoid portion of the internal carotid artery (ICA), the carotid siphon via a transorbital approach, the proximal segment of the anterior cerebral artery (A1), and the precommunicating segment of the posterior cerebral artery (P1). The time-averaged peak frequencies (related to blood flow velocity) were used for further evaluation of the Doppler signal.

The statistical method selected for calculating a representative curve showing the time course of the velocity changes was the “spline approximation” procedure. The times were replaced by their arithmetic mean values and the standard deviation for each mean value was calculated. The curves were calculated in such a way that the points of higher reliability were more closely approximated and the points of lower reliability were less so. As a measure for the reliability of a point, the standard error of the mean value for the day in question was used. Each measured value (“day mean value”) thus received a weight, which was inversely proportional to the standard error, so that points of higher reliability were given a greater weight and points of lower reliability less weight. Finally, a “smoothing spline function” based on local cubic polynomials was calculated in such a way that the integral of the error, squared, was minimal (Fig. 1).

In all of the patients, nimodipine was applied intraoperatively to the exposed cerebral vessels to dilate the arterial vasospasm resulting from operative manipulations. Nimodipine was then administered intravenously for 14 days (2 mg/hr) and orally for another 6 days (60 mg four times daily). This schedule was strictly adhered to in 33 patients, while in the other 17 there was a variation of about 1 to 3 days. The balance of the circulating blood volume and red blood cell volume was carefully monitored. Increased experience in assessing the transcranial Doppler findings aided in more effective initiation of early preventive hypertensive therapy for DID’s in order to obtain a perfusion pressure for the brain.

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* Doppler ultrasound recorder, Model TC 2-64, manufactured by EME, Ueberlingen, West Germany.
Results

Transcranial Doppler Frequencies in Normal Subjects

Transcranial Doppler studies in normal subjects have shown that reliable signals from the circle of Willis can be obtained through the skull in all but 6% of cases. The Doppler frequencies (mean time-averaged peak frequencies ± standard deviation, in kHz) which have been related to blood flow velocity were: MCA 1.64 ± 0.43; ICA 1.54 ± 0.39; siphon 1.46 ± 0.44; P1 1.05 ± 0.24; and A1 1.29 ± 0.33. The standard deviation of the frequencies in the individual arteries of patients is small, and there are no significant differences between the right and left cerebral hemispheres (Fig. 2) or between women and men.

Correlation of Inner Vessel Diameter and Blood Flow Velocity

Since using transcranial Doppler ultrasound recordings, we have performed angiography on only a few cases with high Doppler frequency shifts. In eight patients who showed vasospasm on angiography and who had undergone delayed aneurysm surgery, the diameter of the cerebral arteries was measured from the angio-
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grams with the split image-focusing technique described by Huber and Handa. The frequencies were plotted against the corresponding vessel diameters (Fig. 3). An inverse correlation that was statistically highly significant could be established for the MCA (r = 0.7087, p < 0.001) and ICA (r = -0.7583, p < 0.001), but there was only a negative correlation of low statistical significance in A1 (r = -0.4671, p = 0.054). All of the eight patients with angiographically proven vasospasm had Doppler frequencies above 3 kHz.

Early Vasospasm Within 72 Hours After a Single SAH

In 50 patients there were no angiographic signs of vasospasm during the first 72 hours after aneurysmal SAH. On the contrary, the vessels even appeared to be dilated (Fig. 4). The transcranial Doppler recordings showed no increase in frequency and therefore no change in blood flow velocity that would correspond to vessel narrowing.

Frequency Changes Between Days 4 and 31 After SAH

A typical example of blood flow changes in the MCA’s is presented in Fig. 5 to demonstrate the time course of the Doppler frequency profile. On the side of the operative transsylvian approach, the frequencies and therefore the blood flow velocities were higher than on the opposite side. The velocities increased during the period from Day 4 to Day 8, then leveled off in a plateau phase with maximum velocities from Day 9 to Day 18. The velocities then decreased to normal values during the following 2 weeks. A temporary increase in velocities could be observed after changing nimodipine administration from intravenous to oral. Between Days 6 and 12, the patient developed symptomatic vasospasm with intermittent low-grade hemiparesis. The Doppler frequencies on the corresponding side were more than 3.5 kHz.

In the patient illustrated in Fig. 6, the maximum systolic frequency was 7.9 kHz on Day 7 (3.2 times the normal level), which corresponds to a velocity of 310 cm/sec (11.2 km/hr). This patient did not develop DID’s and, although the frequency increased as a result of vasospasm, the clinical condition improved from Hunt and Hess neurological Grade III to I by the 9th day after SAH.

The mean time course of frequency changes due to vasospasm in the individual cerebral arteries of 50 patients is presented in Fig. 7. The greatest hemodynamic effect occurred in the MCA and ICA, in contrast to minor changes in the A1 and P1 segments. The frequencies on the operated side were always higher than on the contralateral side. This was statistically significant (p < 0.05) for the MCA on post-SAH Days 6 to 9, 11, 13, 16, 18, and 19 and for the ICA on post-SAH Days 7, 9, 13, 16, and 20. Patients with severe hemorrhage and thick layers of blood in the subarachnoid...
Fig. 4. Angiograms obtained 12 hours after subarachnoid hemorrhage showing middle cerebral artery (MCA) and internal carotid artery (ICA) aneurysms. There is no spasm; all vessels are well filled with contrast medium and are dilated. The corresponding Doppler findings indicate no increased frequency. A1 = first segment of the anterior cerebral artery.

Fig. 5. Time course of Doppler ultrasound frequency changes is shown in both of the middle cerebral arteries (MCA's) after operation on Day 1 following rupture of a carotid bifurcation aneurysm and nimodipine treatment. There is a severe frequency increase (critical spasm) in the left MCA (contralateral to the aneurysm) with delayed ischemic deficits from Days 6 to 12, and moderate (subcritical) vasospasm of the right MCA. In both arteries, slight acceleration can be seen on Day 16 after changing from intravenous (i.v.) to oral (p.o.) nimodipine administration. Clinical status following rupture was determined by the classification of Hunt and Hess.6
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FIG. 6. Time course of Doppler ultrasound frequency changes is recorded after surgery on a left middle cerebral artery (MCA) aneurysm within 72 hours after rupture. Even though the frequencies increased up to Day 10, the clinical status (Hunt and Hess grading system) improved continuously only up to Day 9. Frequencies were higher on the side on which the sylvian fissure was split. Frequencies decreased slowly up to Day 15, then increased from Days 15 to 19 after the intravenous (i.v.) nimodipine administration had been discontinued.

noid space developed more vasospasm than did those with a moderate or minor bleed (Fig. 8). This was statistically significant (p < 0.05) on post-SAH Days 5, 7, 10, 11, 15, 17, and 18.

Thirty-three patients received nimodipine intrave-
nously for exactly 14 days and orally for another 7 days. The Doppler frequencies in the MCA both on the side of surgery and on the contralateral side (Fig. 9) increased temporarily after Days 14 and 21.

Among the first 16 patients in our series, seven

FIG. 7. Mean time course of Doppler ultrasound frequency changes in the different arteries of the circle of Willis on the side of the operative approach (upper) and contralateral (lower) in 50 patients. There is an increase in the first 10 days, then a maximum level is reached on Days 18 and 19, followed by a decrease. Frequencies were higher on the side on which the sylvian fissure was split. SAH = subarachnoid hemorrhage; MCA = middle cerebral artery; ICA = internal carotid artery; A1 and P1 = proximal segments of the anterior and posterior cerebral artery, respectively.
developed DID's, which improved without leaving permanent functional deficits. All seven patients displayed a rapid increase in velocity to above 3 kHz on Day 3 or 4. Statistically, there is no difference between the "DID" group and the rest of the patients, because the standard deviation measured in the other 43 patients is high and the number of DID patients is low. Delayed ischemic deficits occurred between Days 6 and 12, when the Doppler frequencies in the MCA were above 3.5 kHz (Fig. 10). The negative predictive value for DID's is 100%, whereas the positive predictive value is 25% (seven of 28 patients). Based on these results, we categorized the Doppler frequencies of vasospasm for clinical practice as follows. A slight acceleration of up to 2 kHz was defined as in the normal range. This was never observed in the presence of angiographically proven vasospasm. Frequencies between 2 and 3 kHz were termed "subcritical." These velocities were seen in vasospastic patients who did not develop ischemic deficits. Frequencies higher than 3 kHz were interpreted as critical vasospasm, since all of the patients who developed symptoms were in this group. Therefore, preventive hypertensive therapy was initiated when Doppler frequencies increased to more than 3.0 kHz.

Fig. 8. Mean time course of Doppler ultrasound frequency changes recorded in the middle cerebral artery on the side of surgery in 48 patients. In the first 3 weeks, patients with severe subarachnoid hemorrhage (SAH) and thick blood layers in all basal cisterns (SAH Grade III, broken line) showed increased hemodynamic changes compared to those with moderate SAH (SAH Grade II, solid line). The frequency difference is statistically significant (p < 0.05) on post-SAH Days 4, 7, 11, 15, 17, and 18 (asterisks). For SAH grading see Table 2.

Fig. 9. Mean time course of Doppler ultrasound frequency changes recorded in the middle cerebral artery in 33 patients correlated with mode of administration of nimodipine. Until Day 14 after subarachnoid hemorrhage (SAH) nimodipine was administered intravenously (i.v.); it was then given orally until Day 21 when it was discontinued. There was a secondary frequency increase when administration was changed from i.v. to oral.
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FIG. 10. Doppler ultrasound frequencies recorded in the middle cerebral artery (MCA) and the internal carotid artery (ICA) correlated with delayed ischemic deficits (DID's). A rapid frequency increase in the first 6 days after subarachnoid hemorrhage (SAH) to more than 3.5 kHz indicates a risk of ischemia. The points represent the onset of DID's in seven patients. The Doppler frequencies of the other patients never exceeded 3.0 kHz and showed only a slow increase in the first 6 days. The day by day increase of frequencies by about 0.5 kHz is called the Doppler index of DID's. Based on this, the frequencies were divided into normal, subcritical spasm, and critical spasm in this illustration.

Degree of Disability

One patient (2%) died as a result of unintentionally lowered blood pressure during severe vasospasm (Fig. 11). According to the Glasgow Outcome Scale, two patients (4%) were severely disabled, six patients (12%) were moderately disabled, and 41 patients (82%) were able to lead a full and independent life.

Discussion

In transcranial Doppler ultrasound studies of the blood flow velocities in the circle of Willis over time, the different arteries must be recorded at the same depth and with the same angle between the ultrasonic beam and the artery. The latter can be achieved by adjusting the insonation angle to show the highest Doppler shift. When the arteries become narrowed, the blood flow velocity increases; this can be measured by ultrasound since there is a corresponding increase in the Doppler shift. Except in cases of a stenosis or spasm of critical degree, the total velocity (flow volume and pressure) proximal or distal to the narrowed segment will decrease. Because of a compensatory increase in velocity, the blood volume will not change until there is a decrease in diameter of 60% to 80%. These findings pertain to the carotid artery of the neck, and comparable investigations on intracranial arteries have not yet been published. The compensatory frequency acceleration can be better measured by transcranial Doppler ultrasonography than by angiography because the velocity increase is proportional to the second power of the diameter reduction. The compensatory velocity increase in the arteries of the circle of Willis depends to a large degree on the collateral channels. Consequently, a marked spasm of the A1 segment can only produce a slight acceleration, because a normally functioning anterior communicating artery can carry blood from the contralateral side. In contrast, severe spasm of the MCA, which has few collaterals, will produce a marked acceleration (Fig. 12).

In the first 72 hours after SAH no frequency accelerations were observed as a sign of vasospasm. After 72 hours, a relatively rapid frequency increase began and continued from Days 4 to 10. Maximum levels were reached between Days 10 and 20, after which time they decreased. These findings correlate well with the CBF measurements, which indicate a decrease in CBF in the first 14 days after SAH. The patients with a rapid increase of more than 3.5 kHz in frequencies between Days 3 and 7 are in danger of developing DID's (Fig. 10). A daily frequency increase of about 0.5 kHz between Days 3 and 7 after SAH is considered to be a Doppler index of DID's. In these cases we initiate preventive hypertensive therapy, with the systolic blood pressure between 130 and 150 mm Hg in normotensive patients and between 140 and 170 mm Hg in hypertensive patients.

The importance of the blood pressure and cerebral
perfusion pressure in vasospasm is illustrated by the history of one patient, whose data are presented in Fig. 11. This 54-year-old woman had an anterior communicating artery aneurysm and was preoperatively classified as Grade 2 according to Hunt and Hess. A CT scan showed a severe SAH, and an uneventful operation was performed within 24 hours after the bleed. Between Days 8 and 12 the patient was treated with induced hypertension because of vasospasm with Doppler frequencies of 4 kHz in the MCA and a slight hemiparesis on the left side. After evacuation of a delayed epidural hematoma, an unintentional drop in systolic blood pressure to 60 mm Hg for 2 hours occurred. After this event, the patient became comatose and CT showed an infarction of the right cerebral hemisphere. The transcranial Doppler recording revealed a reverberating flow pattern with a net flow of zero, a typical sign of brain death.

The theory that washing out clots from the subarachnoid space will diminish the severity of vasospasm could not be proven, because in the region where clots were removed (that is, on the side of the operative approach) there were consistently higher frequencies with a more rapid increase than on the other side (Figs. 7 and 8). The highest velocities were reached in both hemispheres on Day 11 or 12. This may be due to the fact that the vasoconstrictive substances may act faster and more effectively on the cleaned vessels than on vessels with intact arachnoid sheets. Knowing this, we remove only as much subarachnoid blood as is necessary to provide a good operative view. The interrelationship between the severity of SAH and vasospasm (namely, the more blood the more spasm) is clearly illustrated in Fig. 8.

Fig. 12. Angiograms and Doppler ultrasound frequency profiles 9 days after subarachnoid hemorrhage. Morphologically, there is nearly the same lumen narrowing in the internal carotid artery (ICA), the A1 segment of the anterior cerebral artery (ACA), and the middle cerebral artery (MCA). The velocity increase is highest in the MCA because it has very few collateral vessels.

Fig. 13. Doppler ultrasound frequency ranges recorded from the middle cerebral artery (MCA) on the side of surgery in 50 patients following acute aneurysm operation. Only 16% are in the normal range, while the other 84% show a moderate or severe frequency increase. SAH = subarachnoid hemorrhage.
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There are two possible explanations for the secondary acceleration that results from changing the mode of nimodipine administration: 1) a lowered nimodipine level reduces the dilatation of the small resistance vessels, decreases the collateral flow, and induces a higher flow with faster velocities through the spastic arteries; and 2) dilatation of the spastic large basal arteries is reduced with a lower nimodipine level and subsequent flow velocity acceleration.

Angiography is associated with a high morbidity and mortality risk in cases of vasospasm. If the procedure is no longer necessary to evaluate the existence and severity of vasospasm, the individual reactions of the different arteries of the circle of Willis as a result of this procedure is no longer necessary to evaluate the existence and severity of vasospasm.

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