Intracranial Venous Hemodynamics in Patients With Midline Dislocation Due to Postischemic Brain Edema

Erwin Stolz, MD; Tibo Gerriets, MD; Sait Seymen Babacan, BS; Marek Jauss, MD; Jörg Kraus, MD; Manfred Kaps, MD, PhD

Background and Purpose—Cerebral venous pressure is governed by intracranial pressure, cerebral perfusion pressure, and venous outflow resistance. Therefore, changes in venous flow velocities are to be expected because of changes in intracranial pressure and brain tissue dislocation in patients with ischemic stroke and space-occupying brain edema.

Methods—In 21 prospectively recruited patients with middle cerebral artery stroke and postischemic edema, flow velocities in the basal veins, the vein of Galen, the straight sinus, and the P2 segment of the posterior cerebral artery were recorded every 0.9 ± 0.5 days during the first 5 days after symptom onset with the use of transcranial color-coded duplex sonography. The midline shift of the third ventricle was determined by B-mode imaging.

Results—We observed an initial increase of flow velocity in the basal vein ipsilateral to the lesion, followed by a significant decrease within 5 days after symptom onset and with increasing midline shift in patients with brain herniation. In the straight sinus, flow velocity showed a biphasic U-shaped response to increasing dislocation of the third ventricle, with an initial decrease followed by an increase in the course of mass movement (midline shift 1 to 1.5 cm). A steep increase of flow velocity in the vein of Galen took place with a midline shift > 1.5 cm. In the survivors these changes could not be observed. Flow velocity in the P2 segment of the posterior cerebral artery followed a typical course in neither the fatal cases nor the survivors.

Conclusions—Monitoring of flow velocities in the basal cerebral veins and in the straight sinus can provide additional pathophysiological information in patients with space-occupying brain edema after acute stroke. (Stroke. 2002;33:479-485.)

Key Words: brain edema • cerebral veins • intracranial pressure • stroke • ultrasonography, Doppler, color • ultrasonography, Doppler, transcranial

Under normal conditions the intracranial pressure (ICP) is uniform throughout the craniospinal axis. Pathological conditions such as acute mass lesions can lead to a compartment syndrome due to the anatomic subdivision of the craniospinal cavity by the falx, cerebellar tentorium, and foramen occipitale magnum, resulting in a pressure gradient and a mass movement of brain tissue. Although characteristic changes of Doppler velocity spectra recorded from the basal cerebral arteries in intracranial hypertension have been recognized for more than a decade,1,2 little is known about the behavior of intracranial veins in space-occupying stroke.

The cerebral veins can be regarded as collapsible tubes with a flow resistance governed by intracranial and cerebral perfusion pressure and venous outflow resistance.3 Therefore, alterations of venous flow velocities related to changes of ICP can be expected in raised ICP. Furthermore, severe midline distortion may cause changes in flow velocities due to compression of the basal veins in the midbrain cistern and/or possible cufﬁng of the vein of Galen joining the straight sinus (Figure 1). This would imply that the basal veins and the straight sinus are good candidates for monitoring purposes. Recent advances in transcranial ultrasound technique allow the noninvasive examination of the deep cerebral veins and the posterior fossa sinuses.4–6 We therefore applied this method to obtain closer insights into the cerebrovenous circulation during increasing brain tissue dislocation in ischemic stroke.

Subjects and Methods

Patients
In 21 ischemic stroke patients (mean age, 65 ± 12 years; 6 women, 15 men [female/male ratio, 0.4]) with space-occupying edema, flow velocities in the basal vein, the great cerebral vein of Galen, the straight sinus, and the P2 segment of the posterior cerebral artery (PCA) were monitored by transcranial color-coded duplex sonography (TCCS) to record flow velocity changes. Demographic and clinical data of these patients are summarized in the Table.

The patients were enrolled prospectively with a deﬁned time of onset of symptoms and a Scandinavian Stroke Scale score of < 35 to recruit patients with potentially large lesions. During the first 5 days
after the acute stroke, the patients were monitored every 0.9 ± 0.5 days on average. Twelve patients survived, and 9 patients died because of brain stem herniation.

During measurements, systemic arterial blood pressure was maintained in the range of 140 to 180 mm Hg systolically and 70 to 100 mm Hg diastolically. Eleven of the patients were mechanically ventilated, with a maximum positive end-expiratory airway pressure of 6 mbar. Arterial CO₂ partial pressure was kept in the range of 30 to 40 mm Hg. None of the patients showed any relevant cardiopulmonary failure.

The study was performed in accordance with the institutional guidelines and was reviewed by the responsible ethics committee. All patients provided informed consent.

Ultrasound Examination Technique

The intracranial venous system was insonated through a temporal acoustic bone window as described earlier, with the use of a phased array color-coded ultrasound system (Hewlett Packard, Sonos 2000 and 5500) equipped with a 2.0-MHz transducer. In short, the deep cerebral veins were examined at an insonation window depth of 10 cm. The basal vein follows the course of the PCA and was insonated adjacent and superior to the P2 segment in its postpeduncular portion. Then depth was adjusted so that the contralateral skull adjacent and superior to the P2 segment in its postpeduncular portion. The probe was then tilted to the level of the third portion. Then depth was adjusted so that the contralateral skull adjacent and superior to the P2 segment in its postpeduncular portion.

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Data Evaluation

For each venous vessel, peak systolic (PSV) and end-diastolic (EDV) flow velocities were recorded. Because of difficulties in construction of envelope curves around the venous Doppler spectra, no mean flow velocities were measured. Venous flow velocities were recorded without angle correction.

Venous flow velocities were subjected to further analysis by calculating pulse amplitude (PA) (PA = PSV − EDV), systolic/diastolic ratio (Systolic/Diastolic Ratio = PSV/EDV), and resistance index (RI) (RI = PA/PSV). The flow velocity recordings of the P2 PCA were processed in the same way.

A common disadvantage of Doppler indices is the dependence on heart rate. During the observation period, variability of heart rate in the critically ill patients (range, 150 to 55 bpm) was of course unavoidable. As expected, we observed a physiological decrease of heart rate with increasing ICP in most of the patients.

Flow velocities and changes of Doppler indices over time or in relation to the MLS were evaluated as classified data (time: days 1, 2, 3, 4, and 5; MLS(a) < 0.5 cm, MLS(b) 0.5 to 1 cm, MLS(c) 1.1 to 1.5 cm, MLS(d) 1.6 to 2 cm, MLS(e) 2.1 to 2.5 cm). For comparison of data of different groups, a nonparametric Mann-Whitney U test was used. Multiple comparisons were performed with a Kruskal-Wallis test. Relationships of measurements with MLS or time as continuous variables were described by a linear regression model. In addition, we performed a multivariate regression and a common factor analysis to examine the influence of age, sex, MLS, and time on venous and arterial flow velocities.

For comparison of flow velocities in healthy subjects, 54 age- and sex-matched controls (mean age, 66 ± 6.2 years; female/male ratio, 0.41) were selected from a previously published study on venous normative data.

Results

Midline Shift

The MLS of the third ventricle increased linearly with time (Figure 2). The increase of MLS was more rapid and correlated better with time in patients with a fatal outcome due to herniation (r = 0.88, SD = 0.29, n = 56, P < 0.0001) than in the survivors (r = 0.18, SD = 0.27, n = 124, P < 0.05). The steepness of this regression was significantly (P < 0.001) greater, and hence MLS progression was faster in patients with fatal outcome (0.28 ± 0.02 cm/d) than in the group of surviving patients (0.01 ± 0.003 cm/d). MLS significantly differed between survivors and patients with a fatal course on days 2 to 5 (P ≤ 0.01).

<table>
<thead>
<tr>
<th>Demographic and Clinical Characteristics of Ischemic Stroke Patients With Midline Dislocation</th>
<th>Survivors</th>
<th>Fatal Courses</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
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<td>63.8 ± 11.8</td>
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<td>Sex, M/F</td>
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<td>6/3</td>
<td>0.52</td>
</tr>
<tr>
<td>SSS score on admission, median (range)</td>
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<td>6 (5–7)</td>
<td>0.21</td>
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<tr>
<td>Infarct size and location</td>
<td>MCA 3/3</td>
<td>MCA + ACA 3</td>
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<td></td>
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<tr>
<td></td>
<td>MCA &lt;1/3</td>
<td>5</td>
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</tbody>
</table>

SSS indicates Scandinavian Stroke Scale; MCA, middle cerebral artery; and ACA, anterior cerebral artery.
Venous Flow Velocities

Time Course

Basal Veins

In patients with a fatal outcome we observed a distinct pattern of flow velocity changes (Figure 3, top). In a comparison of healthy subjects and fatal cases, flow velocities in the basal vein ipsilateral to the lesion were already significantly lower on day 1 ($P<0.05$), followed by an increase on day 2 and a gradual decrease of flow velocities again over the observation period (days 3, 4, and 5; $P<0.01$). The increase of flow velocities on day 2 was not due to an averaging effect but could be observed in the individual time courses of flow velocities of all fatal cases (data not shown). The extent of this flow velocity increase was independent of the MLS (Spearman’s rank correlation, $P>0.4$). Statistical evaluation of flow velocities on different days of the observation period within the group of patients who died of brain herniation yielded significant results for comparisons of day 5 with days 3 ($P<0.05$), 2 ($P<0.01$), and 1 ($P<0.01$); of day 4 with day 2 ($P<0.01$); and of day 3 with day 2 ($P<0.05$). No statistically significant changes were found for flow velocities in the basal vein on the symptomatic side when we compared the different measurement time points within the group of survivors (Figure 3, top), with the exception of flow velocities on day 5, which were significantly lower ($P<0.05$) than normal values. The contralateral basal vein displayed significantly lower flow velocities on day 5 ($P<0.05$) compared with normal values in the patient group with fatal courses; no significant deviations from normal flow velocities were found in survivors. A paired comparison of flow velocities in the ipsilateral and contralateral basal vein disclosed significant differences for measurements on days 1 ($P<0.01$), 3 ($P<0.01$), 4 ($P<0.01$), and 5 ($P<0.01$) in the fatal cases. No significant differences were found in survivors.

Vein of Galen and Straight Sinus

In both the vein of Galen and the straight sinus, we observed an increase of flow velocities on day 5 in the group of fatal cases that was not present in survivors (Figure 4). Whereas flow velocities on days 1 to 4 did not differ significantly in the vein of Galen, flow velocities on day 5 were significantly ($P<0.05$) higher both compared with days 1 to 4 and

Figure 2. Time course of MLS in survivors and fatal cases. Subjects with lethal courses: $r=0.88$, SD=0.29, $n=56$, $P<0.0001$, steepness $b=0.28\pm0.02$; survivors: $r=0.18$, SD=0.27, $n=124$, $P<0.05$, steepness $b=0.01\pm0.003$.

Figure 3. Time course of PSV in the basal veins (BV) (top) and the P2 segment of the PCA (bottom) for survivors and fatal cases. Error bars represent SD of measurements.

Figure 4. Time course of PSV in the straight sinus (SRS) and the vein of Galen (VG). Error bars represent SD of measurements.
compared with normal values. The observed trend in the straight sinus was not statistically significant.

**P2 Segment of PCA**

Within-group comparison did not reveal significant differences of flow velocities in the ipsilateral and contralateral P2 PCA on days 1 to 5 for either fatal cases or survivors (Figure 3, bottom). Compared with normal values, only flow velocities in the P2 PCA on the lesion side on day 5 in herniated patients were significantly lower ($P < 0.05$). In both patient groups, flow velocities in the ipsilateral and contralateral P2 PCA did not differ significantly from each other.

**Influence of MLS on Venous Flow Velocities**

**Basal Veins**

As expected with a dependence of MLS on time, we observed a decrease of flow velocities in the ipsilateral basal vein in the herniated patients similar to their course over time (Figure 5, top) [MLS(a)→MLS(b to e), $P < 0.05$; MLS(b)→MLS(c to e), $P < 0.05$]. For all MLS classes ≥0.5 cm, flow velocities were significantly lower than normal ($P < 0.01$). In the contralateral basal vein, only flow velocities with MLS >2 cm were significantly lower than normal, and only flow velocities with MLS >1.5 cm were significantly lower compared with the other MLS classes. Flow velocities in the contralateral basal vein were significantly higher than those on the lesion side for MLS classes b and c ($P < 0.01$).

In the survivors, no MLS >1.6 cm was observed. In these subjects, flow velocities in the different MLS classes did not differ significantly in either the ipsilateral or the contralateral basal vein or compared with normal (Figure 5, top).

**Vein of Galen and Straight Sinus**

In patients with a fatal course, flow velocities in the vein of Galen started to increase at MLS >1.5 cm, with a surge at MLS >2 cm (Figure 6, top). This steep increase was significant ($P < 0.05$) compared with flow velocities in the MLS classes <2 cm (Figure 6, bottom). Flow velocities remained unchanged in the survivors.

The straight sinus displayed a flow velocity peak at MLS 1.1 to 1.5 cm (Figure 6, top), followed by a secondary decrease. This flow velocity peak was highly significant ($P < 0.01$) compared with flow velocities within the other MLS classes and was not observed in the surviving patients.

**P2 Segment of PCA**

With increasing MLS, the flow velocities in the P2 PCA on the lesion side gradually decreased in patients with brain herniation (Figure 5, bottom). Increasing MLS had only minor effects on flow velocities on the contralateral side. Compared with normal values, flow velocities in MLS classes

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**Figure 5.** PSV in the basal veins (BV) (top) and the P2 segment of the PCA (bottom) for survivors and fatal cases in relation to MLS of the third ventricle. Error bars represent SD of measurements.

**Figure 6.** PSV in the straight sinus (SRS) and the vein of Galen (VG). Top, PSV of all patients in relation to MLS; bottom, PSV separated by patient groups.
d and e on the symptomatic side were significantly lower (P<0.01). On the contralateral side, flow velocities did not differ significantly from normal. Comparison of flow velocities within the different MLS classes did not reveal significant differences on either the symptomatic or the asymptomatic side.

**Doppler Spectral Changes**

With increasing MLS, PA of the basal vein slightly decreased on the symptomatic side (r = −0.19, P<0.05) but remained unchanged on the contralateral side of the lesion. RI and the systolic/diastolic ratio displayed insignificant changes. The PA of the vein of Galen correlated with MLS (r = 0.35, P<0.01); again, systolic/diastolic ratio and RI did not show significant alterations. No systematic changes of PA, systolic/diastolic ratio, and RI were observed in the straight sinus in relation to MLS. A similar dependence on time was found for the different pulsatility indices of veins and sinuses.

The PA in the ipsilateral and contralateral P2 PCA increased insignificantly in relation to MLS. Systolic/diastolic ratio (r = 0.36, P<0.01; r = 0.25, P<0.01) and RI (r = 0.38, P<0.01; r = 0.19, P <0.05) increased significantly for both the symptomatic and asymptomatic sides, respectively. No correlation of PA, systolic/diastolic ratio, and RI was found over the first 5 days.

**Multivariate Analysis**

Because a strong relationship between time and MLS was apparent, at least in the patients with a fatal course, we examined the effect of age, sex, MLS, and venous as well as arterial flow velocities corrected for the influence of time with a multivariate partial regression analysis. In the total patient cohort, time correlated only with flow velocities in the contralateral basal vein (r = −0.29, β weight = −0.31, P<0.01). A correlation with MLS was found for age (r = 0.28, β weight = −0.13), flow velocities in the basal vein on the symptomatic side (r = −0.27, β weight = −0.04, P<0.05), flow velocities in the vein of Galen (r = 0.67, β weight = −0.07, P<0.01), and flow velocities in the contralateral P2 PCA (r = 0.27, β weight = −0.10, P<0.05). The low β weights result from the limited influence of time on the other variables. When analysis was restricted to subjects with fatal courses, time correlated only with MLS (r = 0.75, β weight = 0.83, P<0.01).

Factor analysis in the total patient cohort identified only 1 factor with an eigenvalue >1. Variables with a loading >0.1 were flow velocities in the vein of Galen (0.83), MLS (0.78), and flow velocities in the ipsilateral P2 PCA (−0.30). Two factors with an eigenvalue >1 were found when common factor analysis was restricted to the fatal cases. Factor 1 comprised MLS (0.97), time (0.92), flow velocities in the vein of Galen (0.68), and flow velocities in the contralateral basal vein (−0.56). Factor 2 constituted sex (−0.65), flow velocities in the ipsilateral basal vein (−0.74), and flow velocities in the straight sinus (0.58). With the use of these 2 factors as new variables in a multiple partial regression model controlled for time, MLS correlated significantly only with factor 1.

**Discussion**

Changes in middle cerebral artery flow pattern in elevated ICP have been known for more than a decade. However, little is known about changes in cerebral venous hemodynamics in response to elevated ICP. Studying cerebral veins in this regard is intriguing because the anatomic situation of the basal vein of Rosenthal in the intracranial midbrain cistern makes local changes of venous hemodynamics due to brain tissue dislocation likely. Moreover, a close relationship between increasing ICP due to postischemic edema and venous blood flow is to be expected. Venous TCCS is a new technique that allows the noninvasive assessment of venous flow velocities and midline dislocation at close time intervals at the patient’s bedside. This was an indispensable prerequisite for this study because frequent transportation to CT or MR tomography sites would not have been possible in patients requiring intensive care treatment.

The methodology used in this study has been sufficiently evaluated. Large sets of venous normative data have been previously published with the use of either TCCS or transcranial Doppler sonography, with excellent agreement among the different studies. The interobserver and intraobserver reliability of venous flow velocity measurements is high (2 SD confidence intervals for non–angle-corrected PSV measurements: basal vein, ± 2.4/± 3.2 cm/s; vein of Galen, ±2.6/± 2.6 cm/s; straight sinus, ±3.3/± 3.2 cm/s), so that the results obtained in this study cannot be explained by chance variations. The reported alterations in the straight sinus and vein of Galen cannot be explained by an angle error occurring with increasing MLS because with an average length and width of the skull of approximately 18 × 13 cm and an observed MLS of < 3 cm in this study, a MLS of 3 cm would result in an angle error of 16° at maximum. With the flow velocity being a function of the cosine of the insonation angle, this would result in a flow velocity measurement error of 4%. The sonographic measurement of MLS has been validated against CT with a 2 SD confidence interval of 1.7 mm.

Similar to the previous findings in the arterial system, we were able to observe distinct alterations of intracranial venous hemodynamics in patients with postischemic space-occupying edema. Consistent with previously published data, MLS showed a steep increase over time in patients who died of brain herniation. The MLS increase was significantly slower in survivors.

The interpretation of intracranial venous hemodynamics must include multiple important denominators, such as cerebrovenous outflow resistance, systemic blood pressure, and especially cerebral perfusion pressure. Additionally, flow velocity does not necessarily reflect flow volume.

Venous flow velocity alterations were only small in patients who survived, even with the MLS increasing up to 1.5 cm. The decrease of flow velocities in the basal vein, especially in response to increasing MLS in the fatal cases, can be explained by decreasing cerebral perfusion pressure. However, the relatively smaller changes in P2 PCA flow velocities and the side-dependent behavior of the basal vein flow velocities make additional causative factors likely. In particular, the flow velocity increase in the vein of Galen and straight sinus cannot be explained by changing cerebral perfusion pressure.
The marked decrease of flow velocities in the basal vein on the lesion side in lethal courses preceding herniation may be explained by a local partial compression of the basal vein at the transition from the prepeduncular to the postpeduncular part. The observation of Schoser and coworkers, who reported increasing flow velocities in the prepeduncular basal vein with increasing ICP, supports our hypothesis.

The basal vein runoff territory partly overlaps with the middle cerebral artery supply. Conceivably, fatal cases had the largest infarcts. Therefore, the initial decrease of flow velocities in the basal vein in fatal cases compared with normal values as well as the side difference in basal vein flow velocities can be explained by a deceased runoff blood volume on the lesion side. Although a local compression of cortical bridging veins at the inflow to the superior sagittal sinus may increase the drainage of blood along transcortical and Sylvian fissure collaterals to deep cerebral veins, the most likely explanation for the short-lived increase of flow velocities in the basal vein on the lesion side on day 2 is a hyperemic response in the middle cerebral artery territory.

The flow velocity increase in the straight sinus and vein of Galen over time and the distinct response of both venous vessels to the extent of the MLS in lethal courses suggest the following explanation: the increasing MLS (in this study 1 to 1.5 cm) leads to a partial collapse of the straight sinus dural wall, resulting in an increase of flow velocities and explaining the essentially U-shaped relationship between flow velocities and MLS. A further increase of MLS (>2 cm) compromises the vein of Galen with an upward and sideways movement of the vein and a functional stenosis at the transition into the fairly rigid straight sinus. A functionally relevant stenosis in the vein of Galen, however, will cause the flow velocities in the straight sinus to drop again. A similar partial collapse of dural sinus structures was reported for the transverse sinus and the middle portion of the superior sagittal sinus in patients with space-occupying edema due to intracerebral tumors and subdural and epidural hematoma. In all cases, partial collapse was confirmed by direct sinography with normalization after treatment. Since the contrast medium was injected directly in the superior sagittal sinus, only the venous runoff was opacified, so that these studies reported no data on the straight sinus. However, our ultrasonographic findings are in agreement with Shakhnovich, whoasoned the straight sinus through an occipital bone window by conventional transcranial Doppler ultrasonography in patients with supratentorial tumors. An increase of flow velocities in the straight sinus could be observed in 12 of 14 patients. Schoser et al. reported a tight relationship between straight sinus flow velocities and ICP in patients with stroke and head trauma. However, these studies lack the dimension of the time course of changes or information on MLS.

Although time and MLS seem to be closely entwined, multivariate analysis showed that there is little effect of the time course beyond the MLS. Therefore, besides the falling cerebral perfusion pressure in progressive postischemic edema, our data may be explained by the actual mechanical effect of increasing MLS. Whether ICP gradients causing the MLS might also have influence on venous flow velocities is purely speculative because we have no data to support this assumption.

Surprisingly, no side-related differences or significant changes in response to time after symptom onset or to extent of MLS were found for the RI in the different venous structures, while RI of the P2 PCA increased significantly on the side of the lesion. This discrepancy is explained best by the Starling resistor theory, which predicts that cerebral veins cannot undergo global collapse—as opposed to a local compression—in response to rising or falling ICP despite changing flow volumes in relation to the driving pressure gradient. Closed cranial window studies in animals were not able to detect a collapse of cortical veins even when the ICP reached the systemic blood pressure.

Although ultrasound follow-up studies in critically ill patients are methodologically very demanding, we were able to detect systematic alterations of cerebral venous hemodynamics in patients with space-occupying postischemic edema that allow us to hypothesize regarding the underlying pathophysiology. Furthermore, our results suggest that altered venous hemodynamics may have a role in the course of late stages of postischemic edema. Indeed, in 55 patients who died of transtentorial brain herniation, Scheinker found that the distribution of mesencephalic lesions was primarily influenced by venous compression. Histological examination revealed congested small veins and capillaries surrounded by hemorrhage and edema. Similar results were reported by Cannon. We hope that our data will stimulate further research in this field. More data on the complex role of venous hemodynamics in elevated ICP may provide better understanding of the mechanism of brain herniation and may help to develop strategies against it.

References


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