A positron emission tomography study of cerebrovascular reserve before and after shunt surgery in patients with idiopathic chronic hydrocephalus

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**Object.** In this study the authors use positron emission tomography (PET) to investigate cerebral blood flow (CBF) and cerebrovascular reserve (CVR) in chronic hydrocephalus.

**Methods.** Ten patients whose mean age was 67 ± 10 years (mean ± standard deviation [SD]) were compared with 10 healthy volunteers who were 25 ± 3 years of age. Global CBF and CVR were determined using 15O–H2O and PET prior to shunt placement and 7 days and 7 months thereafter. The CVR was measured using 1 g acetazolamide. Neurological status was assessed based on a score assigned according to the methods of Stein and Langfitt.

Seven months after shunt placement, five patients showed clinical improvement (Group A) and five did not (Group B). The average global CBF before shunt deployment was significantly reduced in comparison with the control group (40 ± 8 compared with 61 ± 7 ml/100 ml/minute; mean ± SD, p < 0.01). In Group A the CBF values were significantly lower than in Group B (36 ± 7 compared with 44 ± 8 ml/100 ml/minute; p < 0.05). The CVR before surgery, however, was not significantly different between groups (Group A = 43 ± 21%, Group B = 37 ± 29%). After shunt placement, there was an increase in the CVR in Group A to 52 ± 37% after 7 days and to 68 ± 47% after 7 months (p < 0.05), whereas in Group B the CVR decreased to 14 ± 18% (p < 0.05) after 7 days and returned to the preoperative level (39 ± 6%) 7 months after shunt placement.

**Conclusions.** The preliminary results indicate that a reduced baseline CBF before surgery does not indicate a poor prognosis. Baseline CBF before shunt placement and preoperative CVR are not predictive of clinical outcome. A decrease in the CVR early after shunt placement, however, is related to poor late clinical outcome, whereas early improvement in the CVR after shunt placement indicates a good prognosis.

**Key Words** • chronic hydrocephalus • cerebral blood flow • cerebrovascular reserve • positron emission tomography

The diagnosis of hydrocephalus is commonly based on neurological examination, computerized tomography (CT) scanning, or magnetic resonance tomography, and the assessment of cerebrospinal fluid (CSF) dynamics. Additionally, measurement of cerebral blood flow (CBF) has been believed to facilitate the surgical decision-making process. Cortical mapping of CBF was predominantly performed using single photon emission studies. The results were inconsistent: Larsson, et al., stated that the ratio between the perfusion in the frontal and that in the occipital region was helpful in prognostication. Tanaka, et al., postulated that impairment of global CBF in patients with hydrocephalus indicates poor clinical outcome after surgery for shunt placement. In contrast, in a previous positron emission tomography (PET) study it was suggested that a reduction in global CBF was associated with a good prognosis posttreatment.

The estimation of the cerebrovascular reserve (CVR) as a response of cerebral autoregulation is an important additional parameter for characterizing the vascular state and has been revealed to be useful in a number of clinical problems such as in trauma research and in cerebrovascular disease. Some data on the CVR capacity in patients presenting with symptoms of normal-pressure hydrocephalus have been reported. Based on Xe-CT studies, however, Meier, et al., reported that the CVR was preserved only in the early stages of the disease. Because the stimuli of CVR preservation were different, the results are not quite comparable: xenon inhalation, application of angiotensin-converting enzyme, CSF tapping, and administration of acetazolamide elicit different physiological reactions.

Because the results of CBF and CVR measurements in chronic hydrocephalus are still contested, we performed a PET investigation to study the patients’ cerebrovascular status before and after shunt treatment. Because measuring CBF by using 15O–H2O–PET is a unique modality for performing quantitative studies in ischemic diseases of the brain, this method was used together with administration of acetazolamide for CVR mapping.

In this study we deal with the specific question of whether CBF and/or CVR capacity prior to or within a short interval after surgery in patients with chronic hydrocephalus is related to the late clinical outcome of shunt treatment.
Clinical Material and Methods

Protocol and Patient Population

We studied five women and five men with a mean age of 67 ± 10 years (range 49–77 years) who had been scheduled for ventriculoperitoneal (VP) shunt placement on presentation with symptoms of chronic hydrocephalus (gait disturbances, mental deterioration, and urinary incontinence). All patients exhibited at least two of the typical symptoms, among which gait disturbances prevailed. The onset of clinical symptoms occurred at 6 months to 5 years before surgery. All patients underwent cerebral CT or magnetic resonance tomography to verify enlargement of the ventricular system; obliteration or dilation of the cerebral sulci at the convexity and/or periventricular low density were considered signs of disturbed CSF absorption. Before surgery, continuous intracranial pressure (ICP) monitoring was performed for at least 48 hours (for example, to detect pathological wave complexes). Additionally, the CSF outflow resistance (Rout) was measured by intrathecal infusions of sterile isotonic saline given at a constant rate of 90 ml/hour. The pressure volume index (PVI) was evaluated as a measure of the intracranial compliance by administering intrathecal bolus injections. In all patients a medium-pressure valve was inserted (Pudenz-Schulte; Medtronic, Inc., Minneapolis, MN). The CBF was measured before surgery and approximately 1 week and 7 months postsurgery.

Neurological Scoring

Clinical outcome was assessed using neurological scoring for gait and mental disturbances according to the classification system of Stein and Langfitt, based on the degree of functional disturbance.Each symptom was scored with numbers ranging from 0 (none) to 4 (no capacity for independent function). Both numbers were then added, and if urinary incontinence was present another point was added to the sum. This sum was termed the “impairment score.” Clinical status pre- and postsurgery was classified by the same surgeon. A decrease in the impairment score of three or more points postsurgery was regarded as clinical improvement. By this definition, five patients had improved (Group A) and five had not (Group B) at an interval of 7 months after the initial investigation.

Mapping CBF With PET

Measurements were performed under standardized conditions after the patients had rested for 15 minutes. Their ears and eyes were open during the procedure. Informed consent was obtained from the patients or their guardian.

Annihilation photons were registered with a PET scanner (ECAT 951/31; Siemens, Erlangen, Germany). Thirty-one slices with a plane separation of 3.4 mm were obtained simultaneously. The axial and transaxial resolution of the reconstructed images (Hann-filter, cut-off frequency 0.4, 128 × 128 matrix) was approximately 7 to 8 mm full width at half maximum. After a bolus injection of 3.7 GBq 15O-labeled water, multiple sequential periods were recorded (12 × 5 seconds, 4 × 15 seconds, 2 × 30 seconds, and 2 × 60 seconds). The total scan period was 5 minutes. The method for synthesis and the automated procedure for the application of the 15O-labeled water has been described previously. All images were corrected for attenuation (10-minute transmission) and decay during the reconstruction procedure. Radial artery blood samples (1 ml) were taken in the middle of each time interval of the frame mode acquisition, except for one sample that was taken immediately before the scan. The samples were counted in a well counter that was cross-calibrated to the PET scanner. The decay-corrected values were transferred to a computer workstation (SUN 4; Sun Microsystems, Palo Alto, CA) for further data processing. The CBF was calculated (in ml/100 ml/minute) from the time course of tissue and blood activity by using a one-compartment Kety–Schmidt model, and displayed on parametric flow maps. Corrections for delay and dispersion of input function have been described by Van den Hoff, et al. Data sets from different investigations and from different patients were reoriented using the orbitomeatal line.

Regional and global CBF analysis was based on the region-of-interest technique on a representative slice at the level of the basal ganglia. Regions of interest were manually defined as corresponding to the territories of the anterior cerebral artery, the middle cerebral artery, and the posterior cerebral artery of both hemispheres, based on the atlas of Talairach and Tournoux. Gray and white matter were not differentiated because the actual imaging resolution did not provide reliable identification of white matter due to the enlargement of the ventricular system. The CVR capacity was determined after intravenous administration of 1 g acetazolamide over 5 minutes. To guarantee CBF mapping during maximum vasodilation of cerebral vessels, repeated activity recordings were begun after an interval of 15 minutes postinjection.

**TABLE 1**

Neurological score, ICP, and CSF dynamics compared with clinical outcome in 10 patients with chronic hydrocephalus

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group A (5 patients)</th>
<th>Group B (5 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>neurological score (preop)</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>22.0 ± 8.1</td>
<td>22.8 ± 14.3</td>
</tr>
<tr>
<td>Rout (mm Hg/ml/minute)</td>
<td>8.5 ± 2.1</td>
<td>6.3 ± 2.5</td>
</tr>
<tr>
<td>PVI (ml)</td>
<td>47.0 ± 40.3</td>
<td>39.0 ± 20.4</td>
</tr>
</tbody>
</table>

* Values are presented as the mean ± SD. The preop neurological score was assessed according to the method of Stein and Langfitt.

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The CVR was determined as the relative difference in the CBF at baseline and during stimulation (percentage of change).

**Control Volunteers**

Reference values for global baseline CBF were obtained from 10 healthy volunteers (three women and seven men). Their ages ranged from 24 to 33 years, with a mean age of 25.7 ± 2.9 years. The mean CBF was 61 ± 8 ml/100 ml/minute and ranged from 50 to 72 ml/100 ml/minute.

**Statistical Analysis**

Group differences (controls and Groups A and B) and changes in baseline CBF or CVR capacity were tested by using a one- or two-tailed, paired or unpaired Student’s t-test. For significant findings, the specific probability value is noted. Values are expressed as the mean ± 1 SD.

**Results**

**Neurological Scoring, ICP, and CSF Dynamics**

**Presurgery**

The ICP ranged from 7 to 42 mm Hg (22 ± 11 mm Hg), the R\textsubscript{m} from 4 to 11 mm Hg/ml/minute (7 ± 2 mm Hg/ml/minute), and the PVI from 14 to 93 ml (43 ± 30 ml). The neurological scores ranged from 6 to 10 (median 8).

By conventional clinical methods, that is, scoring the neurological impairment, no differences were found in the CSF dynamics (R\textsubscript{m} and PVI) between Groups A and B (p > 0.05; Table 1).

**Global CBF and CVR Presurgery**

Global CBF values in all patients were significantly reduced in comparison with the control group: 40 ± 8 compared with 61 ± 8 ml/100 ml/minute, respectively (p < 0.01). Regarding outcome groups, both Group A (36 ± 7 ml/100 ml/minute) and Group B (44 ± 8 ml/100 ml/minute) had significantly lower global CBF presurgery compared with the control group (p > 0.05; Fig. 1). In comparing outcome groups we found that the reduced global baseline CBF in Group A was significantly different from that in Group B: 36 ± 7 compared with 44 ± 8 ml/100 ml/minute, respectively (p < 0.05). The CVR, however, was no different in either outcome group: 43 ± 21% and 37 ± 29%, respectively (Fig. 2).

**Global CBF and CVR Postsurgery**

Within both outcome groups global baseline CBF levels (in ml/100 ml/minute) did not change 7 days and 7 months postsurgery: 34 ± 6 and 32 ± 10 (Group A) and 41 ± 8 and 32 ± 6 (Group B), respectively (p > 0.05; Fig. 1).

In contrast with baseline CBF, CVR capacity varied. The CVR in Group A increased: 52 ± 37% after 7 days and 68 ± 47% after 7 months. The CVR increase after seven months was statistically significant compared with preoperative values (43 ± 21%, p < 0.05). In Group B the CVR decreased significantly within 7 days postsurgery (14 ± 18 compared with 37 ± 29%, p > 0.05) and returned to the preoperative level after 7 months (39 ± 6%, Fig. 2). The observed differences in CVR between outcome groups at 7 days postsurgery were significant: 14 ± 18% in Group B compared with 52 ± 37% in Group A (p < 0.05). However, the differences in CVR after 7 months did not reach statistical significance: 39 ± 6% in Group B and 68 ± 47% in Group A.

The relative changes in CVR after surgery for shunt placement compared with preoperative values and expressed as the average CVR ratio were significantly different between the outcome groups: 0.45 in Group B and 1.3 in Group A (p < 0.05). Again, after 7 months the differences did not reach statistical significance: 1.04 in Group B and 1.72 in Group A.

**Discussion**

Because vascular status is regarded as a determinant for neurological status in patients with hydrocephalus, we suggest that investigators use measures of the vascular system as criteria for the selection of treatment.47

The CBF and CVR capacity are important parameters of the functional status of the cerebrovascular system.23 In cerebrovascular disease, local or regional deficits of CVR are characteristic alterations.30,36,38,41 Because chronic hydrocephalus may affect global CBF by impairment of CSF circulation, as indicated by experimental animal studies,29 abnormalities in CBF and CVR are expected to occur throughout cerebral territories.5,6 Therefore, global CBF and CVR can be assumed to reflect adequately alterations in the cerebrovascular system in chronic hydrocephalus.

In this study we questioned whether global CBF and CVR capacity can be correlated to late clinical outcome when studies are performed presurgery or within a short interval postsurgery.

We have demonstrated that global baseline CBF was significantly reduced in all patients with hydrocephalus compared with a healthy control group. Because the mean ages were different in each group, the potential influence of age on CBF must be taken into account.10,18,24,38 Leenders, et al.,18 have investigated a normal population of sufficient size to correlate CBF with age. Using the same PET methodology, their values were in the same range as in our study.

On average, CBF decreased by 0.5% per year of age.
Even if this relationship is taken into account, baseline CBF in patients with hydrocephalus was definitely lower (approximately 20% on average) than would be expected in an age-adjusted population.

The relevant result, however, is that low CBF values before shunt surgery did not indicate a poor prognosis, as we already suggested in our previous study. Instead, baseline CBF presurgery was lower in patients with good clinical outcomes than in patients who did not improve after shunt surgery. This difference cannot be explained by an age effect, because there was no significant difference in the mean ages between both outcome groups (66 compared with 69 years of age).

Furthermore, the CVR capacity before shunt deployment had no predictive value, whereas an early increase of CVR after shunt placement was related to a good prognosis. An early decrease of CVR, however, indicated poor outcome. These PET findings are all the more important because they were the only predictors of outcome: values for Rmax and the PVI were not related to clinical outcome.

Neurological Scoring and CBF Mapping With PET Studies

The late clinical outcome was evaluated 7 months post-surgery because it has been shown that within the first 6 months after shunt insertion considerable changes in clinical status may occur. To classify patients in a group of responders and nonresponders we assigned a score obtained using the methods of Stein and Langfitt in patients with normal-pressure hydrocephalus. This score is a modified Barthels and Katz Index of activities of daily living. Because this index is subject to a certain degree of observer bias, we postulated that a minimum decrease of 3 points is required to indicate an improvement in an individual patient’s neurological status. We further postulated that the neurological status had not improved when the score was not changed by more than one point or when it increased.

Follow up of global and regional CBF is not only hampered by technical limitations inherent in the different modalities used but is also influenced by varying physiological and psychological conditions and/or environmental factors present during measurement. In particular, varying activation of cortical areas as a result of the individual’s mental and cognitive status may influence local distribution. Therefore, all possible steps were taken to standardize the conditions under which PET studies were performed (that is, a resting period before pharmaceutical injection, and so on).

Despite this standardized investigation protocol it must be assumed that subsequent investigations may result in CBF values showing small systematic differences. Consequently, differences observed in follow-up studies of CBF and CVR can only be assigned to therapeutic effects if there are significant differences between patients with evidence of clinical improvement and those with no improvement.

Despite the abovementioned methodological limitations the data of our preliminary study indicate that responders and nonresponders after VP shunt insertion differ in their vascular status (baseline CBF and CVR) before and after shunt treatment and furthermore that abnormal baseline CBF before surgery in patients might be associated with a favorable outcome.

In contrast to the work of Meier, et al., who postulated preoperative differences in CVR in patients with and without beneficial effects after VP shunt placement, we did not observe significant differences in the outcome groups regarding CVR before surgery. However, the determination of outcome by using the pretreatment CVR parameter has not been validated.

Other contradictory findings were reported by Tanaka, et al., who postulated an association between clinical improvement after VP shunt insertion and preserved baseline CBF together with impaired CVR, whereas our data showed that decreased baseline CBF together with a preserved CVR is not associated with poor outcome after shunt placement. The data in their study were based on the Xe-washout method, which may be affected by the pharmacological effect of xenon and which is dependent on the individual Xe distribution volume. A vasodilatory and narcotic effect of the contrast medium has been reported.

Conclusions

From our study we conclude that baseline CBF and CVR values presurgery are not definitely predictive of the clinical outcome. Early after VP shunt insertion, however, both parameters of cerebrovascular function may be useful in predicting clinical long-term response to shunt surgery. Because of the preliminary character of this study and the small number of patients included, the potential clinical utility of consecutive CBF and CVR measurement cannot yet be determined. However, it appears justified to expand the data base to investigate the predictive accuracy of CVR capacity after VP shunt placement.

References

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