Is There a Direct Link Between Cerebrovascular Activity and Cerebrospinal Fluid Pressure-Volume Compensation?

Christina Haubrich, MD; Zofia Czosnyka, PhD; Andrea Lavini, MD; Piotr Smielewski, PhD; Rolf R. Diehl, PhD; John D. Pickard, FmedSci; Marek Czosnyka, PhD

Background and Purpose—Cerebral blood flow is coupled to brain metabolism by means of active modulation of cerebrovascular resistance. This homeostatic vasogenic activity is reflected in slow waves of cerebral blood flow velocities (FV) which can also be detected in intracranial pressure (ICP). However, effects of increased ICP on the modulation of cerebral blood flow are still poorly understood. This study focused on the question whether ICP has an independent impact on slow waves of FV within the normal cerebral perfusion pressures range.

Methods—Twenty patients presenting with communicating hydrocephalus underwent a diagnostic intraventricular constant-flow infusion test. Blood flow velocities in the middle cerebral artery and posterior cerebral arteries were measured using Transcranial Doppler. Pulsatility index, FV variability of slow vasogenic waves (3 to 9 bpm), ICP, and arterial blood pressure were simultaneously monitored.

Results—During the test, ICP increased from a baseline of 11 (6) mm Hg to a plateau value of 21 (6) mm Hg (P=0.00005). Although the infusion did not induce significant changes in cerebral perfusion pressures, FV, pulsatility index, or index of autoregulation, the magnitude of FV vasogenic waves at plateau became inversely correlated to ICP (middle cerebral artery: \( r = -0.58, P<0.01 \); posterior cerebral arteries: \( r = -0.54, P<0.01 \)).

Conclusions—This study shows that even moderately increased ICP can limit the modulation of cerebral blood flow in both vascular territories within the autoregulatory range of cerebral perfusion pressures. The exhaustion of cerebrospinal fluid volume buffering reserve during infusion studies elicits a direct interaction between the cerebrospinal fluid space and the cerebrovascular compartment. (Stroke. 2007;38:2677-2680.)

Key Words: cerebral blood flow ■ Doppler ■ hemodynamics ■ neurosurgery ■ neurosurgery

Slow vasogenic waves and derived parameters carry valuable information on the prognosis in patients with intracranial hypertension after brain injury.1–3 Although it has been suggested that intracranial hypertension might suppress slow vasogenic waves by compromising cerebral autoregulation,4 the effects of increased intracranial pressure (ICP) on the modulation of cerebral blood flow are poorly understood. In severe traumatic brain injury the literature indicates no significant time delay between occurrences of vasogenic waves directly without altering cerebral autoregulation. The homeostatic vasogenic activity is reflected in slow waves of cerebral blood flow velocity (FV) and ICP.5 This observation could imply a direct interaction between cerebrospinal fluid (CSF) space and cerebral vasculature, which so far has not been examined. Therefore, our study focused on the question whether mean ICP may influence FV vasogenic waves directly without altering cerebral autoregulation. The objective was to verify whether moderately increased ICP at levels of normal cerebral perfusion pressures (CPP) could specifically affect the amplitudes of vasogenic waves in FV and ICP. In addition, we compared the impact of increased ICP on vasogenic waves in middle cerebral artery (MCA) and posterior cerebral artery (PCA) territories.

This study involved a controlled ICP increase via volume loading of the ventricular spaces, which is routinely applied for diagnosis of disturbed CSF circulation in hydrocephalus and assessment of intraventricular shunt function.6 Setting enables to simultaneously monitor transcranial Doppler and ICP. The relationship was compared between MCA and PCA territories, which even under normal conditions differ in amplitudes of vasogenic waves.7

Methods
Twenty patients (10 female, 10 male, mean age 51, range 21 to 78) with a longstanding history (3 ± 1 years) of CSF circulatory disorder (normal pressure hydrocephalus [n = 9]; post-traumatic hydrocephalus [n = 6]; idiopathic intracranial hypertension [n = 5]) were studied. Patients underwent CSF infusion testing which is a routine clinical method for the accurate analysis of CSF dynamics using constant-rate infusion into CSF space.6,8 The examination was approved by the Local Ethical Committee, and written informed individual consents were obtained.

The intraventricular infusion of Hartmann’s solution (standard compound sodium lactate) at a rate of 1.5 mL/min was initiated after 5 minutes of baseline measurements, and infusion was continued.

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until a steady-state intracranial pressure plateau (equilibrium between infused and resorbed CSF) was achieved. If the ICP reached the plateau or exceeded 40 mm Hg, then the infusion was stopped. ICP, arterial blood pressure (ABP), and FV were recorded at ICP baseline, plateau, and after cessation of saline infusion, until ICP decreased to steady baseline levels. ICP was continuously monitored via a pressure transducer at a saline/filled tube connected to the intraventricular catheter or shunt antechamber. Arterial blood pressure was monitored noninvasively using a servo-controlled finger plethysmograph (Finapres 2300, Ohmeda). The hand was kept steady at the level of the heart during the entire recording. Cerebral blood flow in the left MCA and right PCA were measured with transcranial Doppler (DWL-MultiDop, DWL). 2-Mhz probes were held in position using a headband (Marc 600, Spencer Tech).

Waveforms of ICP, ABP, FV, and cerebral perfusion pressure (CPP=ICP-ABP) were digitalized and captured with a sampling rate of 50 Hz on a personal computer running ICM+ software (http://www.neurosurg.cam.ac.uk/icmplus).

The pulsatility index was assessed according to Gosling.6 As an index of the compensatory reserve of CSF space, we determined the correlation coefficient between pulse amplitude of ICP and mean ICP (RAP).6,8 An RAP close to 0 indicates a good compensatory reserve, whereas an RAP close to +1 indicates an exhausted compensatory reserve.

The further analysis was focused on slow vasogenic waves in the range of 3 to 9 cpm which are induced by peripheral sympathetic regulation and are transferred to cerebral circulation.5 They were detected using fast fourier transformation of simultaneous recordings of ABP, ICP and FV. Slow wave amplitudes in ABP, FV, and ICP were calculated as the coefficient of variation (CoV) and in percent deviation from the mean.9 As an index of cerebral autoregulation, the correlation coefficient index of autoregulation between vasogenic waves of FV and CPP mean was calculated.2 Positive correlation coefficients of index of autoregulation >0.4 signify a positive association of FV and CPP, ie, disturbed autoregulation. Index of autoregulation ≤0.2 can be interpreted as good normal autoregulation.

All values are given as mean ± SD. For the comparison between baseline and plateau, we applied the mixed between-within subjects ANOVA using SPSS. A mixed linear model was applied for analysis of the multiple interdependencies between amplitude measures of slow waves, pulsatility index, and ICP. Statistical significance was set at P < 0.05.

### Results

Twenty data files depicting time courses of ICP, ABP and FV (MCA and PCA) during 5-minute baseline ICP and during 5-minute ICP plateau were included in analysis (mean values; Table 1). All but 1 patient exhibited normal baseline ICP of <13 mm Hg. Infusion study in each patient led to mainly moderately increased ICP plateau reaching from 9.6 to 30.9 mm Hg. Correspondingly, index of autoregulation at both infusion study baseline and plateau did not indicate a significant impairment of cerebral autoregulation (Table 2). The mean values of CPP, FV, and pulsatility index in the MCA and PCA did not show any significant differences between baseline and plateau. ABP at plateau levels was slightly but not significantly larger than baseline (Table 1). However, CSF reserve differed significantly between baseline and plateau indicated by index RAP increasing from values around 0 at baseline to +1 during infusion (Table 2).

Amplitudes of vasogenic waves revealed a similar relation between both vascular territories at baseline and ICP plateau, with larger magnitude in the PCA-FV than the MCA-FV (Table 1). At baseline, ABP slow-wave amplitudes were significantly correlated with slow waves in PCA and MCA (MCA: r = 0.64; PCA: r = 0.56; Figure, A). At infusion study plateau, however, neither of these parameters was correlated with ABP slow vasogenic waves. Infusion study plateau elicited an inverse correlation between slow-wave amplitudes in FV of both vascular territories and ICP mean (MCA: r = −0.59; PCA: r = −0.55; Figure, B). Moreover, a significant correlation was elicited between ICP mean and ICP vasogenic waves (r = −0.711; Table 3).

### Discussion

With exhausted CSF reserve due to intraventricular volume load at plateau of infusion, ICP seems to have direct impact on low frequency oscillations in cerebral blood flow. ICP affected slow-wave amplitudes in MCA and PCA without changing the earlier reported fact that PCA slow waves are relatively larger than MCA slow waves.7 According to current knowledge, the hemodynamic impact of an intracranial hypertension becomes clinically relevant with a reduction of CPP < 65 mm Hg, and loss of autoregulatory reserve. These parameters are considered as hemodynamic indicators of an unfavourable outcome in head injury.5 Infusion study plateau in patients with communicating hydrocephalus showed, however, that ICP and vascular slow waves are negatively correlated even at normal levels of CPP.

Our observations imply a direct interaction between the cerebral vasculature and CSF space, which has not been considered in traditional models of intracranial hypertension so far. Because of this direct impact of ICP increase on

### Table 1. Physiological Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Plateau</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP, mm Hg</td>
<td>11.46±5.55</td>
<td>20.73±6.39*</td>
</tr>
<tr>
<td>ABP, mm Hg</td>
<td>83.61±16.70</td>
<td>90.04±21.69</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>74.77±14.69</td>
<td>76.30±18.59</td>
</tr>
<tr>
<td>FV-MCA, cm/s</td>
<td>61.97±17.40</td>
<td>59.29±18.03</td>
</tr>
<tr>
<td>FV-PCA, cm/s</td>
<td>35.25±8.81</td>
<td>33.12±9.19</td>
</tr>
</tbody>
</table>

All values are mean ± SD. *Significant differences (P < 0.05) between baseline and plateau.

### Table 2. Parameters Derived From Flow Velocity, ICP, and ABP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Plateau</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoV-MCA, %</td>
<td>3.19±1.36</td>
<td>3.29±0.83</td>
</tr>
<tr>
<td>CoV-PCA, %</td>
<td>4.60±1.38*</td>
<td>4.91±1.12*</td>
</tr>
<tr>
<td>CoV-ICP, %</td>
<td>0.57±0.74</td>
<td>0.63±0.34</td>
</tr>
<tr>
<td>RAP</td>
<td>0.11±0.20</td>
<td>0.89±0.08**</td>
</tr>
<tr>
<td>PI-MCA</td>
<td>0.96±0.20</td>
<td>1.07±0.32</td>
</tr>
<tr>
<td>PI-PCA</td>
<td>1.08±0.28</td>
<td>1.20±0.35</td>
</tr>
<tr>
<td>Mx-MCA</td>
<td>0.07±0.33</td>
<td>0.20±0.27</td>
</tr>
<tr>
<td>Mx-PCA</td>
<td>0.06±0.26</td>
<td>0.17±0.26</td>
</tr>
</tbody>
</table>

CoV indicates coefficient of variance or variability in the slow wave range analyzed for FV in the left MCA and the right PCA as well as in ICP; PI, pulsatility indices. All values are mean ± SD. *Significant differences (P < 0.05) between MCA and PCA, and **between baseline and plateau.
cerebral blood flow, slow vasogenic waves in FV lost their relation to systemic blood pressure waves. Whereas at baseline FV slow waves correlated with blood pressure slow waves, at infusion study plateau they seemed to be determined by mean ICP. Infusion study plateau and baseline did not only differ in mean ICP. Both states differed also concerning the CSF compensatory reserve. In contrast to baseline, the RAP values at infusion study plateau were close to 1 which is in line with the literature. These values indicated an exhausted CSF compensatory reserve in every patient irrespectively of the pathogenesis of hydrocephalus being either post-traumatic, normal pressure hydrocephalus, or idiopathic intracranial hypertension.

Results point toward a new aspect of the interaction between ICP and FV, which has been proposed recently by Hu et al. They observed a specific decrease in vascular low frequency dynamics after the decline in compliance of the space surrounding the vessel. Their study suggested that when reserves of this space are exhausted, vascular compliance would be compromised as well. Giller et al have already proposed that the vascular compliance determines the input impedance and therefore the magnitude of slow spontaneous oscillations in flow velocity.12

The literature showed that severe intracranial hypertension after head injury is associated with an amplitude reduction of ICP slow waves.1 This study’s observation implies that the exhaustion of CSF volume–buffering reserve compromises the cerebrovascular compliance already at ‘sub-critical’ ICP before altering CPP or cerebral autoregulation. Therefore, we hypothesize that the inverse correlation of FV slow-wave amplitudes with mean ICP level might provide an early indicator of intracranial hypertension. Further studies assessing the impact of ICP increase on FV vasogenic waves in traumatic brain injury, subarachnoid hemorrhage, and stroke are needed.

Conclusion
When the CSF volume–buffering reserve is exhausted, the amplitudes of slow waves in MCA-FV, PCA-FV, and ICP significantly depend on mean ICP. Even moderately increased ICP can limit the modulation of cerebral blood flow in the middle and posterior vascular territories without altering autoregulation. This observation may suggest a direct interaction between the CSF space and the vascular compartment.

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Disclosures
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