Impaired Cerebral Vasomotor Activity in Spontaneous Intracerebral Hemorrhage

Jennifer Diedler, MD; Marek Sykora, MD; André Rupp, PhD; Sven Poli, MD; Georg Karpel-Massler, MD; Oliver Sakowitz, MD; Thorsten Steiner, MD

Background and Purpose—Impairment of cerebrovascular autoregulation may promote secondary brain injury in acute brain insults. Until now, only limited data are available on autoregulation in patients with spontaneous intracerebral hemorrhage. In the current study, we aimed to investigate cerebrovascular reactivity and its significance for outcome in spontaneous intracerebral hemorrhage.

Methods—We continuously recorded mean arterial pressure, intracranial pressure, and cerebral perfusion pressure for 95 hours in 20 patients with spontaneous intracerebral hemorrhage. The moving correlation coefficient between mean arterial pressure and intracranial pressure (pressure reactivity index), an index of cerebral vasoreactivity, was calculated from the available artifact-free monitoring time (mean, 50.4 hours).

Results—In the univariate analysis, pressure reactivity index (r = 0.66; P = 0.002), hemorrhage volume (r = 0.62; P = 0.007), cerebral perfusion pressure (r = -0.71; P = 0.001), mean arterial pressure (r = -0.61; P = 0.005), and hematoma growth (r = 0.53; P = 0.02) significantly correlated with National Institutes of Health Stroke Scale Score at discharge. In a multivariate stepwise linear regression model, pressure reactivity index remained the only independent predictor of outcome (β = 0.659; P = 0.004). In the subgroup of patients with pressure reactivity index greater than a functional threshold of >0.2, the correlation between mean cerebral perfusion pressure and outcome remained significant (r = -0.73; P = 0.0102), whereas National Institutes of Health Stroke Scale Score at discharge did not correlate with cerebral perfusion pressure in patients with pressure reactivity index <0.2 (r = -0.05; P = 0.9078).

Conclusions—We found evidence for impaired cerebral vasomotor activity as measured by pressure reactivity index in patients with spontaneous intracerebral hemorrhage. We suggest that impaired cerebrovascular reactivity contributes to poor outcome in intracerebral hemorrhage patients. This effect may be mediated by fluctuations in cerebral perfusion.

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Key Words: cerebral perfusion pressure ■ cerebrovascular reactivity ■ intracerebral hemorrhage ■ neurocritical

Impaired autoregulation of cerebral blood flow has recently been recognized as an important mechanism, predisposing the brain to secondary damage in patients with traumatic brain injury.1,2 Subarachnoid hemorrhage,3,4 or ischemic stroke.5 To date, only limited data are available on cerebral autoregulation in patients with spontaneous intracerebral hemorrhage (ICH).6–8 However, in the light of the ongoing discussion of managing blood pressure and its putative association to hematoma enlargement in acute ICH,9,10 continuous information on the state of cerebral autoregulation may be relevant for therapy. It could help to identify situations where lowering the mean arterial pressure (MAP) eventually leads to concomitant, hazardous lowering of cerebral perfusion pressure (CPP).

Cerebral vasomotor reactivity has been suggested as a key mechanism of autoregulation of cerebral blood flow.11 It is defined as the ability of vascular smooth muscle to respond to alterations in transmural pressure.12 To assess cerebral vasomotor reactivity, Czosnyka et al13 investigated the correlation between slow wave changes in MAP and intracerebral pressure (ICP) by calculating the pressure–reactivity index (PRx) in patients with traumatic brain injury. A positive PRx implies a positive association between the slow components of MAP and ICP, which is an indicator of passive, nonreactive behavior of the cerebral vessels. However, a negative value was shown to reflect a normally reactive vascular bed where changes in MAP result in inversely correlated changes in ICP within a 5- to 30-second time window. PRx has been validated in several clinical studies.2,13,14 Although it should not be used as a synonym, it has been shown to accurately estimate the status of cerebral autoregulation. Steiner et al15 introduced a PRx-guided concept to determine an individual, optimal cerebral perfusion pressure (CPPopt) in traumatic brain injury patients. They defined CPPopt as the CPP value

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From Department of Neurology (J.D., M.S., A.R., S.P., T.S.), University of Heidelberg, Heidelberg, Germany; Department of Neurosurgery (G.K.-M., O.S.), University of Heidelberg, Heidelberg, Germany.
Correspondence to Jennifer Diedler, MD, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany.
E-mail: Jennifer.diedler@med.uni-heidelberg.de
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under which PRx reached its minimum value and found that outcome was more likely to be favorable in patients with a mean CPP close to CPPopt.

In the current pilot study we assessed cerebrovascular pressure reactivity during the postacute phase (days 1–5) and its significance for outcome in spontaneous ICH (sICH) patients. Taking vasomotor reactivity into account, we sought to determine an individual optimal CPP.

Patients and Methods

Patients

We prospectively included 20 patients with sICH admitted to our neurologic intensive care unit. Inclusion criteria were: (1) sICH and (2) the need for ICP measurement. All patients required intubation and mechanical ventilation and were continuously sedated using midazolam and sufentanil. Therapy was aimed to keep ICP <20 mm Hg and CPP >60 mm Hg, according to current guidelines. Systolic blood pressure was cautiously lowered when >160 mm Hg using continuous infusion of urapidil or metoprolol. Arterial blood gas samples were obtained every 2 hours to adjust ventilation parameters. PaCO2 was maintained between 35 and 45 mm Hg (mean 39.4 ± 2.3 mm Hg). Neurological deficit on admission and at discharge was assessed by the National Institutes of Health Stroke Scale Score (NIHSSS). Hematoma volume was calculated from the first CT or MRI scan using the a x b x c method, where “a” and “b” are the largest perpendicular diameters of the zone of hyperintensity and “c” is the number of sections in which the lesion is present multiplied by the diameter of the sections. Hematoma growth was defined as an increase in the volume of intraparenchymal hemorrhage of >33% on the 1-hour or 24-hour or postoperative CT scan compared with the baseline CT scan.17 Intraventricular bleeding was scored according to the Graeb score.18

Neuromonitoring and Data Recording

Intracranial pressure was measured with an intraparenchymal transducer (Raumedic NEUROVENT; 15 patients) or through an external ventricular drain (5 patients).

Blood pressure was measured from the radial artery (Dräger; Siemens). ICP, systolic and diastolic blood pressure, MAP, CPP, and heart rate were synchronously recorded with a sampling frequency of 1 Hz. The data were stored on a bedside computer (ICU pilot; CMA). Data recording was started after placing of the ICP probe.

Artifact Elimination and Assessment of Cerebrovascular Vasoreactivity

First, data files were cleaned from epochs containing incomplete data recordings and artifacts were visually identified and cut out of the raw data (J.D., M.S.). Incomplete recordings were caused by disturbed interaction between the monitoring system and the recording software or caused by complete disconnection the patient from the monitoring system (eg, during in-house transportations). Artifacts mostly resulted from inadequate pressure signals, for example, during therapeutic cerebrospinal fluid drainage in patients with intracranial ICP recordings. Other frequent artifacts were caused by nursing interventions as positioning of the patient, suctioning, or drawing blood gas probes.

Next, data were resampled to obtain 1 value every 6 seconds. Then, PRx was calculated every 60 seconds as a moving linear regression of MAP and ICP, as described by Steiner and Czosnyka.1,13 For calculation of PRx, only data points fulfilling the criteria of systolic arterial pressure between 60 to 180 mm Hg, MAP between 50 and 120 mm Hg, and ICP >0 mm Hg were included in the analysis. Mean MAP, systolic blood pressure, CPP, and ICP values were calculated from the artifact-free monitoring time but before filtering. All calculations were performed using Matlab (version 7.5).

CPPopt

CPPopt was calculated as described by Steiner et al.1 All recorded CPP values of each patient were divided into groups of 5 mm Hg and corresponding PRx values were averaged (using Fisher-Z transformation) within these groups. CPPopt was defined as the CPP associated with the lowest average value of PRx. Groups containing <2% of the PRx values were excluded from the analysis. The total time period that a patient was within the individual CPPopt range was calculated as percentage of total monitoring time, including all intervals during which the patient was within the range of CPPopt ±0.05 PRx.

Statistical Data Analysis

For all artifact-free episodes, PRx values were calculated as described. The PRx values were pooled for each patient and after Fisher-Z transformation a total mean PRx value was determined. For correlation analyses, Spearman rank or Pearson product moment correlation was used. Because of linearity of the variables, a stepwise multivariate linear regression model was applied to study the associations with the regard on independence. Values of P<0.05 were considered statistically significant in all tests. To characterize the nonlinear relationship between NIHSSS at discharge and PRx, a spline interpolation was applied. All calculations were performed using Matlab (MathWorks, version 7.5). Statistical analyses were performed using the SPSS 16.0 statistical package.

Results

Twenty patients were prospectively included. One patient had to be excluded because the recording time was insufficient because of technical difficulties (only 1.6 hours total monitoring time). Mean total monitoring time in the remaining 19 patients was 95 hours per patient (range, 28–264 hours). The artifact-free recording time was mean 50.4 hours per patient (20.6–94.5 hours). Mean time from onset of symptoms to the start of monitoring was 26 hours.

Individual patient characteristics are listed in Table 1. The mean parenchymal hemorrhage volume was 46.4 mL. Three patients had hematoma growth >33%. Space-occupying hematomas were surgically evacuated in 5 of 20 patients. All except 1 patient presented with concomitant intraventricular hemorrhage; 2 patients presented with purely intraventricular hemorrhage. Mean age was 60.3 years (range, 34–84 years; SD, 14.4), median baseline NIHSSS was 22 (range, 7–34; interquartile range, 13–34), and median NIHSSS at discharge was 24 (range, 6–42; interquartile range, 11 to 33). Three of 19 patients (16%) died during the hospital stay. Thirteen patients (68%) had hypertensive hemorrhage, 3 (16%) had hemorrhage associated with coagulopathy, and 3 (16%) had hemorrhage of other etiologies.

Median PRx of all patients during the entire artifact-free monitoring time was 0.28 (range, −0.19 to 0.80; interquartile range, 0.07–0.35). As an example, Figure 1 demonstrates the minute-by-minute PRx values plotted over the entire monitoring time (a+b) and the distribution of these values (c+d) for a patient with a mean PRx of −0.04 as compared to those of a patient with a mean PRx of 0.41.

In the univariate analysis, NIHSSS at discharge significantly correlated with PRx (r=0.66; P=0.002). Other variables that significantly correlated with NIHSSS at discharge were ICH volume (r=0.62; P=0.007), MAP (r=−0.61; P=0.005), CPP (r=−0.71; P=0.001), and hematoma growth (r=0.53; P=0.02). Age, baseline NIHSSS, or admission blood pressure did not significantly correlate with outcome.
When the effects of PRx on outcome were examined with regard on independence in a stepwise linear regression model, only PRx remained as a significant independent factor ($P=0.004$, $F=11.5$; $r^2=0.43$; Table 2).

Because of the nonlinear behavior of the relationship between PRx and NIHSSS at discharge, we reassessed the data using a spline routine. This resulted in a better fit compared to a linear model ($r^2=0.53$ vs $r^2=0.41$; Figure 2). We thereby defined a functional threshold for impaired cerebrovascular reactivity of PRx $>0.2$. In these patients, we found a significant linear correlation between NIHSSS at discharge and mean CPP ($r=-0.73$; $P=0.011$; Figure 3). In contrast, for patients with PRx values $<0.2$, no correlation was found between outcome and CPP ($r=-0.09$; $P=0.848$; Figure 3).

Table 2. Stepwise Linear Regression Analysis to Predict NIHSSS at Discharge

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta^*$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRx†</td>
<td>0.659</td>
<td>0.004</td>
</tr>
<tr>
<td>MAP</td>
<td>-0.266</td>
<td>0.270</td>
</tr>
<tr>
<td>Mean CPP</td>
<td>-0.301</td>
<td>0.354</td>
</tr>
<tr>
<td>Hemorrhage volume</td>
<td>0.309</td>
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<tr>
<td>Age</td>
<td>0.159</td>
<td>0.450</td>
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<td>NIHSSS on admission</td>
<td>0.254</td>
<td>0.202</td>
</tr>
<tr>
<td>Surgery</td>
<td>-0.123</td>
<td>0.549</td>
</tr>
<tr>
<td>Hematoma growth</td>
<td>0.236</td>
<td>0.265</td>
</tr>
<tr>
<td>Admission blood pressure</td>
<td>0.018</td>
<td>0.939</td>
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</table>

* $\beta$ indicates the standardized partial regression coefficient.
† Only variables with $P<0.05$ entered into the model, $F=11.5$, $P=0.004$, $r^2=0.43$.

For 6 of 19 patients (32%), we were able to determine a CPPopt. Mean CPPopt was 84 mm Hg (range, 75–100 mm Hg). During a mean 30.9% of artifact-free monitoring time, CPP of these patients was in their optimal range. The percentage of time in the range of CPPopt was nonsignificantly correlated to NIHSSS at discharge ($r=-0.62$; $P=0.191$).

**Discussion**

In the current pilot study we were able to continuously assess cerebral vasomotor reactivity in 19 of 20 patients with sICH. We found impaired cerebrovascular reactivity as defined by PRx $>0.2$ in 12 of 19 patients. In these patients, we observed a linear correlation between CPP and outcome. Our PRx threshold is in line with findings from previous studies in traumatic brain injury patients. Czosnyka et al$^{19}$ report that a PRx $>0.2$ for $>6$ hours was associated with fatal outcome in traumatic brain injury patients. Another study including 40 patients with head injuries showed that a PRx value $>0.3$ indicated impaired vasomotor activity. Two previous studies have assessed autoregulation in patients with acute ICH by examining changes in cerebral blood flow (CBF) on drug-induced lowering of MAP. In a SPECT study, Kuwata et al$^3$ measured global and regional CBF after blood pressure was reduced in 68 patients with thalamic and putamina hypertensive ICH at a mean 3 days and 3 weeks after ictus. In the acute phase, autoregulation in the perihematomal zone seemed to be preserved while global CBF significantly decreased in both hemispheres after reducing MAP $>20\%$. In the chronic phase, the opposite was the case: a decrease in MAP did not result in a significant change in global CBF but evoked a decrease in perihematomal CBF.

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Table 1. Individual Patient Characteristics

<table>
<thead>
<tr>
<th>Patient#</th>
<th>Age</th>
<th>Localization</th>
<th>Volume, mL</th>
<th>Graeb Score</th>
<th>Etiology</th>
<th>NIHSSS at Admission</th>
<th>NIHSSS at Discharge</th>
<th>Hypertension</th>
<th>Diabetes</th>
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IVH indicates intraventricular hemorrhage; AVM, arteriovenous malformation.
Powers et al measured CBF using positron emission tomography in 14 patients with acute supratentorial ICH before and after lowering MAP (from 143±10 mm Hg to 119±11 mm Hg) 6 to 22 hours after symptom onset. This group found no significant change in global and perihematomal CBF after lowering the MAP. However, there are substantial differences compared to our study. First, positron emission tomography and single photon emission CT (SPECT) aim to measure cerebral blood flow, whereas PRx is a measure of cerebrovascular reactivity. Second, in contrast to CBF measurements at a selected point in time, PRx was assessed continuously over a longer period of time and without artificially manipulating the MAP. We observed wide fluctuations of PRx in the same patient. This suggests that periods with impaired and intact vasomotor reactivity may coexist. As was found in traumatic brain injury patients, the ratio and overall duration of each seems to be important with regard to outcome.

The current guidelines on treatment of spontaneous ICH recommend a CPP >60 mm Hg for all ICH patients based on data from patients with traumatic brain injury. However, Steiner et al who originally introduced the CPPopt concept in a cohort of 114 head-injured patients found that outcome at 6 months correlated with the difference between CPP and CPPopt. They were able to identify CPPopt in 68 patients (60%). We were able to identify CPPopt in 32% of patients. The percentage of time in which CPP was kept in the range of CPPopt seemed to be linked to outcome but this failed to reach significance. This may be attributable to the small sample size.

A limitation of the current pilot study was sample size. We could only include patients with large hematomas, requiring...
therapy with regard to outcome are warranted. However, reactivity to avoid secondary brain injury. These results suggest that individual CPP management may be particularly important for patients with disturbed vasomotor reactivity as defined by PRx<0.2. We found a significant correlation between NIHSSS and mean CPP in the subgroup of patients (n=11) with PRx >0.2 (r=-0.73; P=0.0102), whereas no correlation (n=7) was found for patients with PRx <0.2 (r=-0.05; P=0.9078). For this analysis, we excluded the patient who died after 28 hours of total monitoring time (mean CPP 1.6 mm Hg outside the physiological range). ICP measurement. Thus, our results are limited to a special subgroup of ICH patients. Moreover, all but 1 patient exhibited ventricular extension. Therefore, we cannot draw conclusions about the state of cerebrovascular reactivity in other cohorts of ICH patients, especially those without intraventricular extension. Moreover, the characteristics of our cohort probably account for the fact that of the classic outcome predictors, only hemorrhage volume but not age, baseline NIHSSS, admission blood pressure, or amount of intraventricular blood correlated with NIHSSS at discharge.

Conclusions
We found a significant correlation between vasomotor reactivity and outcome at discharge. Of clinical importance may be that in the case of impaired vasomotor reactivity as defined by PRx >0.2, CPP correlated significantly with outcome. These results suggest that individual CPP management may be particularly important for patients with disturbed vasomotor reactivity to avoid secondary brain injury. However, clinical trials investigating the benefit of a PRx-guided CPP therapy with regard to outcome are warranted.

Disclosures
None.

References
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