Evidence Against a Perihemorrhagic Penumbra Provided by Perfusion Computed Tomography

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Background and Purpose—Several recent studies analyzing perfusion changes in acute intracerebral hemorrhage fed the debate whether there is secondary ischemic tissue damage in the vicinity of intracerebral hemorrhage. We used perfusion CT to address this question.

Methods—We examined 36 patients between 2001 and 2002 with acute intracerebral hemorrhage (within 24 hours after symptom onset). A subgroup of 8 patients was examined serially on day 1, between days 2 and 4, and after day 5. Nonenhanced CT images and maps of cerebral blood flow, cerebral blood volume, and time to peak were evaluated by region of interest analysis.

Results—In comparison to the contralateral hemisphere, perfusion values were clearly reduced around the hematoma (relative values: cerebral blood flow 0.51, cerebral blood volume 0.62, time to peak 1.7 seconds). There was no difference in size between the area of reduced perfusion and the area of edema (5.17 versus 5.75 cm², respectively) surrounding the hematoma. At time point 2, the edema grew significantly.

Conclusions—In accordance with previous studies, we found reduced perfusion as well as edema surrounding acute intracerebral hemorrhage. Regarding ischemic tissue damage, we did not detect an initial mismatch between the perfusion deficit and the edema and therefore could not identify any tissue at risk of ischemia. We therefore interpret the reduced perfusion as a secondary phenomenon, ie, reduced oxygen demand of tissue damaged by pressure and clot components, not as the cause of any tissue damage associated with acute intracerebral hemorrhage. (Stroke. 2007;38;2941-2947.)

Key Words: computed tomography ■ intracerebral hemorrhage ■ perfusion

In recent years, several studies investigated, with heterogeneous results, whether there is a penumbra surrounding acute intracerebral hemorrhage. The imaging techniques used in these studies included perfusion and diffusion weighted MRI, positron emission tomography, single photon emission computed tomography, and perfusion computed tomography (PCT). Two PCT studies and one using positron emission tomography reported clearly reduced perfusion surrounding acute intracerebral hemorrhage (ICH).1–3 Of 5 studies using perfusion MRI,4–8 3 found a prolongation of the mean transit time,4,7,8 whereas the other 2 did not find any perfusion change in the perihemorrhagic area. One of these studies,6 however, found reduced values of the apparent diffusion coefficient indicative of ischemic damage.

The aim of our study was to clarify whether there is a reduction of cerebral perfusion in the perihemorrhagic area and if so, whether this reduction is as pronounced as in ischemic stroke to account for secondary tissue damage. Because these changes are most likely to occur within a small rim around the hematoma, we considered perfusion CT with its relatively high spatial resolution to be a suitable technique. Another advantage of this technique over MRI is that there are no susceptibility artifacts due to paramagnetic effects of hemoglobin and its degradation products.

Materials and Methods

Patients

Between August 2001 and October 2002, we prospectively examined 54 consecutive patients who were admitted due to acute ICH within 24 hours after symptom onset. Patients were enrolled after ICH was confirmed by nonenhanced CT and written and informed consent was obtained from every patient or their next of kin. The study was approved by the local Institutional Review Board. Eighteen patients had to be excluded post hoc. In 9 cases, ICH turned out to be secondary (eg, due to ischemia) or we found concomitant cerebral pathologies that would potentially have disturbed perfusion analysis (eg, subdural hematoma with mass effect). In the other 9 cases, PCT maps were of inferior quality because of insufficient enhancement or severe patient motion. Finally, 36 patients were included (see Table 1 for demographic and clinical data). A subgroup of 8 patients additionally received follow-up.
These patients were examined 3 times: at day 1 (time point 1: 0 to 24 hours), between days 2 and 4 (time point 2: 24 to 96 hours), and between days 5 and 8 (time point 3: 96 to 192 hours). None of these patients received surgical treatment during the whole period, because we tried to avoid any procedure possibly interfering with edema formation or growth. Because many patients need ventricular drainage, hematoma evacuation, or die in the course of ICH, it was not possible to collect a larger cohort for serial examinations.

**Imaging Protocol**

All patients were examined with a multislice CT scanner (Somatom Volume Zoom; Siemens). The used nonenhanced CT and perfusion CT protocol have been described in detail elsewhere.9,10 Two adjacent 10-mm sections were acquired once every second for 40 seconds at the level of the maximum extent of the hematoma after intravenous injection of a compact bolus of 50 mL nonionic iodinated contrast agent (Ultravist 300; Schering) with a power injector.

**Postprocessing**

Of the 2 PCT sections, we chose the one that best fit the maximum extent of the hematoma; the other one was discarded. Perfusion parameter images (cerebral blood flow [CBF], cerebral blood volume...
[CBV], and time-to-peak [TTP]) were calculated using a commercial PCT package (Neuro Perfusion CT; Siemens) using the maximum slope model installed on a standard workstation (Leonardo; Siemens). Hematoma volumes were determined from nonenhanced CT scans using volume determination software (Volume; Siemens).

Regions-of-interest (ROIs) for the assessment of hypoperfused areas were drawn manually on CBF maps by visual guidance such that they included areas of markedly reduced CBF around the hematoma (see Figure 1). These ROIs were automatically transferred to the CBV and TTP maps. They were drawn such that larger vessels or ventricles were excluded. Another ROI was drawn accordingly on the first PCT image, ie, before contrast arrival, with the aim to assess areas of diminished attenuation, ie, edema on nonenhanced CT (see Figure 1F). For normalization purposes, perfusion parameters were also determined in the contralateral unaffected hemisphere by placing a ROI into the anatomical location corresponding to the hemorrhage site.

Because an important goal was precisely measuring parameter changes over time, we followed the approach used by Koenig et al11 and normalized perfusion parameters to the unaffected hemisphere yielding relative values for CBF and CBV and difference values for TTP. This normalization considerably reduces influences of mathematical model, operator-dependent input function selection, bolus quality, and patient age.

Statistical Analysis
Values are given as mean±SD or median with first and third quartile. For statistical testing, we used a standard software package (SPSS 14). To check for normal distribution, we used the Kolmogorov-Smirnov test. In case of normal distribution, we applied the paired t test and Pearson linear correlation coefficient; if the data did not show a normal distribution, we used Wilcoxon test and the Spearman rank correlation, respectively. Due to the explorative character of this study, we did not adjust for multiple testing. Results are reported as significant if P≤0.05.

Results
See Table 1 for clinical and PCT data. All patients had proof of ICH on nonenhanced CT. For all time points, there was a
significant reduction of CBF and CBV ($P \leq 0.001$) and a significant prolongation of TTP ($P \leq 0.03$) in the perihemorrhagic area compared with the contralateral hemisphere. We did not detect a significant difference between attenuation measurements in the perihemorrhagic area in comparison to the contralateral hemisphere at any time point (data not shown).

**Acute Stage**

Thirty-one (86%) hematomas were located in the deep subcortical gray matter and 5 (14%) in the white matter. Nineteen (52.7%) ICH were in the left hemisphere and 17 (47.3%) in the right one. Seventeen patients also had ventricular hemorrhage; 3 of them required ventricular drainage in the course of the disease. We found no difference in size between the area of edema and the area of reduced perfusion; both quantities were highly correlated (Pearson’s correlation $r = 0.74$, $P = 0.0001$).

Although there was no correlation between hematoma and edema size, hematoma size correlated with the size of the perfusion deficit (Spearman rank correlation, $r = 0.502$, $P = 0.002$). We also found slight but significant correlations between hematoma size and relative CBF values (Spearman rank correlation, $r = -0.401$, $P = 0.02$) and hematoma size and dTTP values (Spearman rank correlation, $r = 0.397$, $P = 0.02$).

Multivariate regression analysis did not reveal any of the variables as a significant predictor of the clinical state at admission as represented by the National Institutes of Health score.

**Serial Examinations**

See Table 2 for serial perfusion CT data. Because our data are derived from 8 individuals only and graphical analysis (not shown) revealed a left-skewed, more logarithmical distribution, we used Wilcoxon’s test to check for differences between time points as well as between groups.

The area of edema significantly increased between the first and second examination (difference $= 1.561 \text{ cm}^2$, $P = 0.025$) and remained at that level. There was no remarkable change over time for the area of the perfusion deficit (Figure 2).

Due to the increase in size of the edema, it differed significantly from the area of the perfusion deficit (difference $= 2.77 \text{ cm}^2$, $P = 0.017$) at time point 2 and still showed a strong trend at time point 3 (difference $= 2.56 \text{ cm}^2$, nonsignificant).

The hematoma volume became continuously smaller among time points 1, 2, and 3 indicating no rebleeding. All perfusion parameters improved between time points 1 and 3: relative CBF increased (difference $= 0.1$, $P = 0.036$), relative CBV increased as well (difference $= 0.11$, $P = 0.012$), and dTTP decreased (difference $= 0.97$, $P = 0.018$; Figure 3).

**Discussion**

Using perfusion CT, we found a significant reduction of perfusion parameters in an area surrounding acute ICH. This is consistent with the literature.1–4,7,8 Our perfusion values agree well with those reported for the perihemorrhagic area by Fainardi and coworkers who used perfusion CT5 (relative CBF: 0.51; relative CBV: 0.61; dTTP: 1.2 seconds; relative values calculated by the authors from absolute values in 3) and with those from Zazulia and coauthors (relative CBF: 0.56) who used positron emission tomography.1 The perfusion reduction is less pronounced than the one reported for infarcted tissue in acute ischemic stroke by König and colleagues (relative CBF: 0.51 versus 0.34; relative CBV: 0.62 versus 0.43; dTTP: 1.76 versus 4.8),11 who used the same PCT method. Supporting results come from 2 perfusion MRI studies,5,6 both using the dynamic-susceptibility-contrast technique, who did not find any prolongation of the mean transit time. A possible explanation therefore can be derived from the results of Rosand et al,2 who found a significant reduction of perfusion only within a 2-mm range around the hematoma but not beyond. Dynamic-susceptibility-contrast-perfusion MRI bases on an echoplanar imaging sequence comprising a T2* decay, which has been shown to overestimate acute ICH in size.12 Therefore, overestimation of hematoma size could have led to missing this small rim using MRI, in which reduced perfusion is likely to occur. This favors PCT over perfusion MRI due to its higher spatial resolution as recently emphasized.13

We were not able to classify the degree of edema by attenuation differences. Although a rim-shaped area of edema could easily be identified visually by both readers independently, we regularly saw hyperattenuation foci within this area due to leakage of hematoma components into it, a finding already described in an animal model.14 Keeping in

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### Table 2. Serial Examination Data*

<table>
<thead>
<tr>
<th></th>
<th>ICH Size (mL)</th>
<th>Edema Area (cm²)</th>
<th>Perf.-Def. area (cm²)</th>
<th>Relative CBF</th>
<th>Relative CBV</th>
<th>Difference in TTP (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First examination 1 to 24 hours after onset</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>23.28±28.71</td>
<td>5.27±2.04</td>
<td>5.24±1.65</td>
<td>0.47±0.07</td>
<td>0.58±0.06</td>
<td>1.85±1.18</td>
</tr>
<tr>
<td>Median (range)</td>
<td>14.1 (6.76–25.52)</td>
<td>4.08 (3.79–7.25)</td>
<td>5.35 (3.77–5.82)</td>
<td>0.47 (0.41–0.49)</td>
<td>0.58 (0.53–0.66)</td>
<td>1.48 (1.17–3.13)</td>
</tr>
<tr>
<td><strong>Second examination 24 to 72 hours after onset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>21.21±25.98</td>
<td>6.84±1.54</td>
<td>5.3±2.05</td>
<td>0.55±0.12</td>
<td>0.66±0.13</td>
<td>0.74±0.59</td>
</tr>
<tr>
<td>Median (range)</td>
<td>11.88 (5.67–24.69)</td>
<td>6.33 (5.71–8.32)</td>
<td>4.85 (3.7–6.72)</td>
<td>0.51 (0.45–0.66)</td>
<td>0.61 (0.56–0.76)</td>
<td>0.63 (0.21–1.16)</td>
</tr>
<tr>
<td><strong>Third examination 72 to 168 hours after onset</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>20.14±26.69</td>
<td>7.19±2.48</td>
<td>5.04±1.5</td>
<td>0.5±0.09</td>
<td>0.72±0.09</td>
<td>0.94±0.91</td>
</tr>
<tr>
<td>Median (range)</td>
<td>9.37 (4.35–24.27)</td>
<td>7.51 (5.54–9.33)</td>
<td>4.95 (3.82–5.77)</td>
<td>0.57 (0.52–0.65)</td>
<td>0.69 (0.65–0.76)</td>
<td>0.51 (0.3–1.55)</td>
</tr>
</tbody>
</table>

*Values of the mean±SD and the median together with the first and third quartile.
mind that attenuation changes due to acute ischemia occur within a very narrow range of approximately 2 Hounsfield units, these hyperattenuation foci confounded the quantitative analysis in the surrounding of a cerebral hematoma.

The motivation behind the ongoing debate regarding a perihemorrhagic zone of reduced perfusion with unclear pathophysiological and clinical relevance is the following: if there indeed is a secondary ischemic pathology, then it should be treated in time.

Tissue at risk of infarction, the so-called penumbra, has been studied extensively in conjunction with acute ischemic stroke. By applying the mismatch concept MRI techniques (diffusion weighted imaging and perfusion MRI) seem to allow to visualize this tissue at risk and to derive therapeutic decisions from this information. The penumbra shows reduced perfusion without infarction unless this state persists too long and the perfusion-restricted tissue develops cytotoxic edema and permanent damage. We did not find this typical temporal sequence in our data. We did not see a difference between the area of edema and the area of reduced perfusion initially. Thus, we could not identify any tissue at risk. Moreover, there was dissociation between the area of edema and the area of reduced perfusion over time instead of an association. The significant difference at the second time point was due to an increase of the size of edema, whereas the area of reduced perfusion remained unchanged over time. This increase 2 to 4 days after bleeding most likely represents extracellular or vasogenic edema, which has been repeatedly reported under these circumstances.

The most convincing argument against ischemic tissue damage around acute ICH can be found in the work of Zazulia and coauthors, who, using positron emission tomography, found a similar reduction of relative CBF as we did in the perihemorrhagic area. This reduction, however, was combined with a reduced, rather than increased, oxygen extraction fraction in contrast to findings in ischemia. This favors diachesis, autoregulatory hypoperfusion due to reduced oxygen demand, as a likely explanation for the observed reductions in CBF. A possible mechanism causing reduced demand is inflammatory tissue damage due to various components of the hematoma that also cause extracellular edema. Consistently, we found a transient increase in size of the edematous area between days 2 and 4, most likely corresponding to extracellular or vasogenic edema.

Another noxious stimulus possibly and immediately leading to reduced perfusion and tissue damage is pressure due to the mass effect exerted by the hematoma. A condition under which pressure damage to brain tissue has been studied extensively in humans and animal models is brain retraction during neurosurgical procedures. Animal studies uniformly report about CBF reductions as well as functional impairment and structural damage due to retractor pressure. In humans, Yundt and colleagues found a reduced oxygen extraction fraction besides a reduction of CBF, again favoring

Figure 2. Time course of the size of the area of reduced perfusion and edema. Shown are mean values for the whole group at each time point together with the standard deviation. The area of edema increased significantly (*P=0.025), whereas the area of reduced perfusion remained the same. Therefore, the area of edema and that of reduced perfusion differed significantly at the second time point (**P=0.017).
Figure 3. Serial differences of perfusion parameters (CBF, CBV, TTP). Shown are mean values for the whole group at each time point together with the standard deviation. CBF and CBV increased between time points 1 and 3; dTTP decreased predominantly between time points 1 and 2.
diathesis over ischemia as the cause of reduced cerebral perfusion. Supporting this theory, we found a positive correlation between the size of the area of reduced perfusion and the hematoma size. In agreement with the findings of Fainardi, we found a moderate negative correlation between hematoma size and relative CBF ($r = -0.401$, $P = 0.02$) and a positive correlation between hematoma size and dTTP ($r = 0.397$, $P = 0.02$).

Conclusions

Our results provide evidence against impending secondary ischemic tissue damage, ie, a penumbra in the area around an acute ICH. Diathesis, initially caused by the pressure exerted by the hematoma and later maintained by toxic clot components that produce vasogenic edema, is a more likely explanation for the perfusion alterations commonly observed in the perihemorrhagic area.

Disclosures

E.K. is an employee of Siemens Medical Solutions, Forchheim, Germany. Siemens Medical Solutions also manufactured the medical equipment used in this study.

References

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