Very Low Cerebral Blood Volume Predicts Parenchymal Hematoma in Acute Ischemic Stroke

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Background and Purpose—Parenchymal hematoma (PH) may worsen the outcome of patients with stroke. The aim of our study was to confirm the relationship between the volume of very low cerebral blood volume (CBV) and PH using a European multicenter database (I-KNOW). A secondary objective was to explore the impact of early reperfusion and recanalization.

Methods—The volume of cerebral tissue with CBV ≤2.5th percentile of the normal hemisphere was calculated within the acute diffusion-weighted imaging lesion. Hemorrhagic transformation was assessed on day 2 MRI according to the European Cooperative Acute Stroke Study II criteria. Recanalization and reperfusion were assessed on 3-hour follow-up MRI.

Results—Of the 110 patients, hemorrhagic transformation occurred in 59 patients, including 7 PH. In univariate analysis, the acute National Institutes of Health Stroke Scale score (P=0.002), acute diffusion-weighted imaging lesion volume (P=0.02), and thrombolysis (P=0.03), but not very low CBV (P=0.52), were associated with hemorrhagic transformation. The volume of very low CBV was the only predictor of PH (P=0.007). Early reperfusion and recanalization had no influence on either hemorrhagic transformation or PH.

Conclusion—Very low CBV was the only independent predictor of PH in patients with acute stroke. (Stroke. 2013;44:2318-2320.)

Key Words: cerebral hemodynamics ▪ hemorrhage ▪ ischemic stroke ▪ perfusion imaging ▪ thrombolysis

Hemorrhagic transformation (HT) is a feared complication of ischemic stroke, especially in the advent of parenchymal hematoma (PH). Lower cerebral blood volume (CBV) may be a marker of HT after revascularization procedure.1 The aim of our study was to confirm the relationship between the volume of very low CBV (VLCBV) and HT using a European multicenter database (I-KNOW). A secondary objective was to explore the impact of early reperfusion and recanalization on the risk of HT.

Methods

Patients

We analyzed patients from the I-KNOW multicenter study, who underwent sequential MRI assessment for acute anterior circulation stroke (http://www.i-know-stroke.eu). Regional ethics committee approved the protocol, and informed consent was obtained from all patients.

MRI Protocol

At admission, all patients underwent diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery, T2-weighted gradient echo, time-of-flight MR angiography, and perfusion-weighted imaging. A repeat MRI, using the same sequences, was performed 3 hours after the first scan to assess early reperfusion (3-hour follow-up MRI). Follow-up examinations at day 2 and 1 month were acquired without perfusion-weighted imaging.

Image Analysis

After motion correction using an in-house developed software, perfusion maps, including CBV, were generated according to the reference method.1 Using a semiautomated software, masks of the acute DWI lesion and the contralateral hemisphere were generated. All perfusion maps and morphological images were coregistered within subjects using MATLAB 2010b (MathWorks Inc, Natick, MA) and SPM8 (Wellcome Trust Centre for Neuroimaging, University College London).

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2318
London, London, United Kingdom). The volume of VLCBV was determined according to a reference threshold previously used (2.5th percentile). HT was assessed on day 2 MRI using the European Cooperative Acute Stroke Study (ECASS II) criteria. The perfusion lesion was defined by a $T_{max} \geq 6$ s. Early reperfusion was a voxel-based, coregistered measurement and required $\geq 50\%$ reduction of the perfusion lesion volume between admission and 3-hour perfusion-weighted imaging. Early recanalization was also graded at 3 hours with the thrombolysis in cerebral infarction criteria.

### Statistical Analysis

Data were described with median and interquartile range values for continuous data and sample size and percentage for categorical data.

### Results

The I-KNOW cohort included 168 patients. Fifty-eight patients were excluded from analyses due to MRI data of insufficient quality (there were no differences between included and excluded patients regarding National Institutes of Health Stroke Scale score and acute DWI lesion volume). Thus, 110 patients were analyzed. Baseline characteristics are presented in Table 1. HT occurred in 59 patients (53.6%): PH was observed in 7 (type 1, 6; type 2, 1) and HI in 52 (type 1, 40; type 2, 12). No PH occurred on 3-hour follow-up MRI. All PH were detected on day 2 MRI.

Univariate analysis showed that the acute National Institutes of Health Stroke Scale score ($P=0.002$), baseline DWI lesion volume ($P=0.02$), and thrombolysis ($P=0.03$) were predictive of HT. No significant association was found between VLCBV and the risk of global HT ($P=0.52$; Table 2). Conversely, focusing on PH and no-PH subgroups, the volume of VLCBV was the only predictor of PH in univariate analysis ($P=0.007$; Table 3). Due to the small number of PH, multivariate analysis was limited to a very small number of variables, among which VLCBV was the only one with final $P<0.05$.

Recanalization was able to be assessed in 81 patients, with 58 (71.6%) patients showing early recanalization. Early recanalization had no influence on either HT ($P=0.24$) or PH ($P=0.52$). Early reperfusion was able to be assessed in 52 patients and was observed in 36 (69.2%) patients. Early reperfusion was not associated with either HT ($P=0.46$) or PH ($P=0.49$).

### Table 1. Baseline Characteristics of Included Patients (n=110)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median or Sample Size [First; Third] Quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 [62–77]</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46 (42.6)</td>
</tr>
<tr>
<td>Male</td>
<td>62 (57.4)</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>6.30 [5.60–8.09]</td>
</tr>
<tr>
<td>Admission NIHSS score</td>
<td>11 [6–16]</td>
</tr>
<tr>
<td>Time to MRI, min</td>
<td>149 [109.8–251.3]</td>
</tr>
<tr>
<td>VLCBV, mL</td>
<td>0 [0–0.33]</td>
</tr>
<tr>
<td>VLCBV-NPH, mL</td>
<td>0 [0–0.316]</td>
</tr>
<tr>
<td>VLCBV-PH, mL</td>
<td>0.18 [0.04–4.13]</td>
</tr>
<tr>
<td>Admission DWI lesion, mL</td>
<td>13.8 [6.6–27.6]</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>67 (62)</td>
</tr>
<tr>
<td>Recanalization,* n (%)</td>
<td>58 (71.6)</td>
</tr>
<tr>
<td>Reperfusion†, n (%)</td>
<td>36 (69.2)</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; NPH, nonparenchymal hematoma; PH, parenchymal hematoma; and VLCBV, very low cerebral blood volume.

*Data available for 81 patients.
†Data available for 52 patients.

To assess the ability of VLCBV to predict HT and PH, univariate and multivariate logistic regression analyses were performed. To select a limited number of relevant variables in multivariate analysis, candidate variables were sequentially eliminated when they did not reach 0.1 significance level. Significance level was set at $P=0.05$ in the final multivariate model. Analyses were performed with R software (R Development Core Team, R: A Language Environment for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; http://www.R-project.org, 2011.)

### Table 2. Logistic Regression for HT Versus No-HT Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.03</td>
<td>(0.99; 1.06)</td>
<td>0.10</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>1.00</td>
<td>(0.98; 1.02)</td>
<td>0.87</td>
</tr>
<tr>
<td>Admission NIHSS score</td>
<td>1.12</td>
<td>(1.04; 1.21)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to MRI, min</td>
<td>1.00</td>
<td>(1.00; 1.00)</td>
<td>0.54</td>
</tr>
<tr>
<td>VLCBV, mL</td>
<td>1.11</td>
<td>(0.80; 1.52)</td>
<td>0.52</td>
</tr>
<tr>
<td>Admission DWI lesion, mL</td>
<td>1.02</td>
<td>(1.003; 1.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Thrombolysis, %</td>
<td>2.46</td>
<td>(1.11; 5.47)</td>
<td>0.03</td>
</tr>
<tr>
<td>Recanalization,* %</td>
<td>1.79</td>
<td>(0.67; 4.73)</td>
<td>0.24</td>
</tr>
<tr>
<td>Reperfusion†, %</td>
<td>1.60</td>
<td>(0.45; 5.76)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DWI, diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hematoma; and VLCBV, very low cerebral blood volume.

*Data available for 81 patients.
†Data available for 52 patients.
Our results are in line with recent studies, where VLCBV was considered a hallmark for impending neuronal death. At these levels of hypoperfusion, severe damage to the microvasculature associated with PH.1,9 Predicting this subtype of hemorrhage is critical when considering a reperfusion therapy.6 Regional VLCBV indicates a critical reduction of cerebral perfusion pressure and is considered a hallmark for impending neuronal death.7 At these levels of hypoperfusion, severe damage to the microvasculature and blood–brain barrier may increase the risk of hemorrhage.8 Our results are in line with recent studies, where VLCBV was associated with PH.19 In addition, revascularization may also promote reperfusion injury. Previous studies on VLCBV suggested that delayed recanalization may favor PH.9 In line with recent reports, we showed no significant influence of early recanalization and subsequent reperfusion on the risk of PH.10,11

The I-KNOW study was not designed to assess the efficacy of intravenous thrombolysis. Treatment allocation was not randomized or otherwise controlled. No conclusion can thus be made on the specific bleeding risks in patients after revascularization procedure.

In conclusion, the present results indicate that a severe reduction of CBV is predictive of PH. Although the number of PH may hamper the significance of the results, National Institutes of Health Stroke Scale score, DWI lesion volume, and thrombolysis showed no specific association with the occurrence of PH.

The distinctive radiological features, prognostic impact, and pathogenesis of PH were previously highlighted.5 Predicting this subtype of hemorrhage is critical when considering a reperfusion therapy.6 Regional VLCBV indicates a critical reduction of cerebral perfusion pressure and is considered a hallmark for impending neuronal death.7 At these levels of hypoperfusion, severe damage to the microvasculature and blood–brain barrier may increase the risk of hemorrhage.8 Our results are in line with recent studies, where VLCBV was associated with PH.19

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In conclusion, the present results indicate that a severe reduction of CBV is independently associated with risk of PH in patients with acute stroke. By identifying patients at risk for this deleterious type of HT, the extent of VLCBV may eventually guide acute treatment decisions after further evaluation in larger patient cohorts.

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**Disclosures**

None.

**References**


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