Reperfusion of Very Low Cerebral Blood Volume Lesion Predicts Parenchymal Hematoma After Endovascular Therapy

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**Background and Purpose**—Ischemic stroke patients with regional very low cerebral blood volume (VLCBV) on baseline imaging have increased risk of parenchymal hemorrhage (PH) after intravenous alteplase–induced reperfusion. We developed a method for automated detection of VLCBV and examined whether patients with reperfused-VLCBV are at increased risk of PH after endovascular reperfusion therapy.

**Methods**—Receiver operating characteristic analysis was performed to optimize a relative CBV threshold associated with PH in patients from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) study. Regional reperfused-VLCBV was defined as regions with low relative CBV on baseline imaging that demonstrated normal perfusion ($T_{\text{max}} < 6$ s) on coregistered early follow-up magnetic resonance imaging. The association between VLCBV, regional reperfused-VLCBV and PH was assessed in univariate and multivariate analyses.

**Results**—In 91 patients, the greatest area under the curve for predicting PH occurred at a relative CBV threshold of <0.42 (area under the curve, 0.77). At this threshold, VLCBV lesion volume $\geq 3.55$ mL optimally predicted PH with 94% sensitivity and 63% specificity. Reperfused-VLCBV lesion volume was more specific (0.74) and equally sensitive (0.94). In total, 18 patients developed PH, of whom 17 presented with VLCBV (39% versus 2%; $P=0.01$), all of them had regional reperfusion (47% versus 0%; $P=0.01$), and 71% received intravenous alteplase. VLCBV lesion (odds ratio, 33) and bridging with intravenous alteplase (odds ratio, 3.8) were independently associated with PH. In a separate model, reperfused-VLCBV remained the single independent predictor of PH (odds ratio, 53).

**Conclusions**—These results suggest that VLCBV can be used for risk stratification of patients scheduled to undergo endovascular therapy in trials and routine clinical practice. *(Stroke. 2015;46:1245-1249. DOI: 10.1161/STROKEAHA.114.008171.)*

**Key Words:** cerebral ■ hemorrhage ■ magnetic resonance imaging ■ perfusion imaging ■ stroke

Parenchymal hematoma (PH) is the most feared complication of reperfusion therapy in acute ischemic stroke. Imaging characteristics that are associated with an increased risk of parenchymal hematoma include a large diffusion-weighted imaging (DWI) lesion, a lesion with a severely prolonged $T_{\text{max}}$, a very low apparent diffusion coefficient, or a very low cerebral blood volume (VLCBV). Among these variables, VLCBV seems to be the best predictor with high sensitivity and moderate specificity for predicting PH after intravenous thrombolysis. Previous studies investigating the association of VLCBV with PH involved manual processing to obtain VLCBV measurements and were based on data from patients treated with intravenous alteplase (intravenous tissue-type plasminogen activator [tPA]). Here, we evaluate whether patients with VLCBV can be identified with automated image processing software, and whether the presence of VLCBV is associated with the development of parenchymal hemorrhage after endovascular reperfusion.

**Methods**

**Patients**

The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) study was a prospective observational study of patients who were treated with endovascular therapy. The eligibility criteria for the DEFUSE 2 study were intention to start endovascular stroke therapy within 12 hours of symptom onset, age $\geq 18$ years, baseline National Institute of Health Stroke Scale (NIHSS) $\geq 5$, and bridging with intravenous alteplase (odds ratio, 3.8) were independently associated with PH. In a separate model, reperfused-VLCBV remained the single independent predictor of PH (odds ratio, 53).
nonpregnant state, premorbid modified Ranking Scale (mRS) ≤2, and no contraindication for magnetic resonance imaging (MRI).³

**Imaging Protocol and Analysis**

A standardized imaging protocol using 1.5 or 3 Tesla MRI systems was used. Patients received 3 scans, such as a baseline MR scan (gradient recalled echo, intracranial magnetic resonance angiogram, diffusion and perfusion sequence obtained within 90 minutes before the start of the endovascular procedure), an early follow-up scan (same sequences as baseline) within 12 hours after the endovascular procedure, and a late follow-up scan (gradient recalled echo, diffusion, and fluid-attenuated inversion recovery) on day 5 or at discharge from the hospital, whichever came sooner.⁴ Additional imaging was obtained as clinically indicated.

Relative cerebral blood volume (rCBV) maps were generated using fully automated image processing software (Rapid Processing of Perfusion and Diffusion [RAPID]).⁵ Relative CBV values were calculated for each pixel by dividing its CBV by a smoothed CBV of its mirror pixel in the contralateral hemisphere. For each patient, the rCBV lesion volume was calculated for each rCBV threshold ranging between 0 and 1 in 0.01 increments. Assessment of rCBV lesions was restricted to areas with rCBV ≥0.18. The rCBV ratio threshold and the rCBV lesion volume threshold that were associated with the best prediction of PH were determined with receiver operator curve analyses and used to define patients who had very low CBV (VLCBV). More specifically, optimal VLCBV criteria were defined by first establishing the rCBV ratio threshold with the largest Youden index. The rCBV ratio threshold and the rCBV lesion volume threshold that were associated with the best prediction of PH were determined with receiver operator curve analyses and used to define patients who had very low CBV (VLCBV). More specifically, optimal VLCBV criteria were defined by first establishing the rCBV ratio threshold with the largest area under the receiver operating characteristic and next, the rCBV lesion volume, at this rCBV ratio threshold, with the highest Youden index.

Regional reperfusion of the VLCBV lesion was assessed by 2 investigators on the coregistered subacute MR perfusion scan, obtained 12 hours after endovascular therapy. It was defined as restoration of perfusion (T_peak <6 s) to reduce artifacts.⁶ The rCBV ratio threshold and the rCBV lesion volume threshold were associated with the best prediction of PH were determined with receiver operator curve analyses and used to define patients who had very low CBV (VLCBV). More specifically, optimal VLCBV criteria were defined by first establishing the rCBV ratio threshold with the largest area under the receiver operating characteristic and next, the rCBV lesion volume, at this rCBV ratio threshold, with the highest Youden index.

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**Statistical Analysis**

Univariate analyses were used to assess the association of clinical and radiological variables with 2 outcome variables, such as VLCBV and PH. Independent predictors of PH were assessed with multivariate analyses. Variables that were significant at an α=0.1 in the univariate analyses were entered in a multivariate logistic regression model. A backward elimination procedure was used, in which variables with an α≤0.05 were eliminated from the model. Separate multivariate models were constructed for VLCBV and reperfused-VLCBV, to avoid the simultaneous inclusion of predictor variables that are closely correlated. For other predictors that are correlated (eg, NIHSS and DWI lesion volume), only the predictor that had the strongest association with PH was included in the multivariate model. Differences in distributions of continuous variables were assessed with the Mann–Whitney U test. For the distribution of the mRS, categories 5 and 6 were collapsed into 1 category. Analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC) and StatsDirect (United Kingdom).

**Results**

The DEFUSE 2 study reported findings on 99 patients.⁶ Of these, 91 patients had adequate baseline and subacute MRI data for assessment of VLCBV, regional reperfusion, and PH. These 91 patients were included in this analysis (Figure 1). The

**Table 1. Characteristics for Groups With and Without VLCBV**

<table>
<thead>
<tr>
<th></th>
<th>VLCBV Present</th>
<th>VLCBV Absent</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>66 (50–75)</td>
<td>74 (54–81)</td>
<td>0.1</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>19 (14–21)</td>
<td>13 (9–18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DWI lesion volume, median (range)</td>
<td>31 mL (2–310 mL)</td>
<td>7 mL (0.5–65 mL)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Target mismatch, n (%)</td>
<td>32 (43)</td>
<td>12 (75)</td>
<td>0.02</td>
</tr>
<tr>
<td>Poor collateral flow, n (%)†</td>
<td>21 (62)</td>
<td>21 (54)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*P values are obtained from univariate logistic regression analysis.
†Poor collateral flow is defined as a score of 0–2 on a 5-point scale.¹²

**Figure 1.** Flow diagram demonstrating risk of parenchymal hematoma. A flow diagram illustrates the risk of parenchymal hemorrhage stratified by the presence of very low cerebral blood volume (VLCBV), regional reperfusion, and pretreatment with intravenous tissue-type plasminogen activator. DEFUSE2 indicates Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2; PH, parenchymal hematoma; and tPA, tissue-type plasminogen activator.
optimal rCBV lesion criteria on baseline MRI to predict PH were an rCBV ratio <0.42 (area under the curve, 0.768) and a volume $\geq 3.55$ mL (Youden index, 0.578). These criteria were implemented in automated perfusion processing software. VLCBV was present on the baseline MRI in 48% (n=44) of the patients. Compared with patients without VLCBV, patients with VLCBV had larger DWI lesions and higher baseline NIHSS scores, whereas collateral rating and age did not differ between groups (Table 1). Among patients with VLCBV, 82% (36 of 44) had regional reperfusion on follow-up PWI and 43% (19 of 44) had global reperfusion (Thrombolysis in Cerebral Infarction 2B-3 scores on their angiogram at completion of the endovascular procedure. NPV indicates negative predictive value; PH, parenchymal hematoma; PPV, positive predictive value; TMM, target mismatch; and VLCBV, very low cerebral blood volume.

**Table 2. Test Characteristics of VLCBV to Predict Parenchymal Hematoma**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>PH+/VLCBV+</th>
<th>PH+/VLCBV−</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLCBV</td>
<td>17/44</td>
<td>1/47</td>
<td>94% (71%–100%)</td>
<td>63% (51%–74%)</td>
<td>39% (25%–54%)</td>
<td>98% (87%–100%)</td>
</tr>
<tr>
<td>VLCBV in TMM</td>
<td>13/32</td>
<td>1/43</td>
<td>93% (84%–100%)</td>
<td>69% (56%–78%)</td>
<td>41% (24%–59%)</td>
<td>98% (86%–100%)</td>
</tr>
<tr>
<td>VLCBV in non TMM</td>
<td>4/12</td>
<td>0/4</td>
<td>100% (40%–100%)</td>
<td>33% (11%–65%)</td>
<td>33% (11%–65%)</td>
<td>100% (40%–100%)</td>
</tr>
<tr>
<td>Regional reperfused-VLCBV</td>
<td>17/36</td>
<td>1/55</td>
<td>94% (71%–100%)</td>
<td>74% (62%–83%)</td>
<td>47% (31%–64%)</td>
<td>98% (89%–100%)</td>
</tr>
<tr>
<td>Global reperfused-VLCBV</td>
<td>9/19</td>
<td>9/72</td>
<td>50% (27%–73%)</td>
<td>86% (76%–93%)</td>
<td>47% (25%–71%)</td>
<td>88% (77%–94%)</td>
</tr>
</tbody>
</table>

Regional reperfused-VLCBV includes patients with VLCBV who have reperfusion of their VLCBV lesion on follow-up PWI. Global reperfused-VLCBV includes patients with VLCBV who have Thrombolysis in Cerebral Infarction 2B-3 scores on their angiogram at completion of the endovascular procedure. NPV indicates negative predictive value; PH, parenchymal hematoma; PPV, positive predictive value; TMM, target mismatch; and VLCBV, very low cerebral blood volume.

**Discussion**

Our results demonstrate that VLCBV is a strong predictor of parenchymal hematoma in patients undergoing endovascular treatment for acute stroke, particularly in the setting of regional reperfusion. The optimal definition for VLCBV was an rCBV lesion of at least 3.55 mL at an rCBV threshold of <0.42. VLCBV defined with these criteria had excellent negative predictive value and moderate positive predictive value for predicting PH, both in patients with and without the target mismatch pattern. Given those test characteristics, the absence

**Table 3. Characteristics of Patients With and Without Parenchymal Hematoma**

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Parenchymal Hematoma (n=18)</th>
<th>No Parenchymal Hematoma (n=73)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>66.1 (14.3)</td>
<td>64.5 (16.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>19 (14–21)</td>
<td>14 (11–19)</td>
<td>0.02</td>
</tr>
<tr>
<td>SBP, mm Hg, mean (SD)</td>
<td>149.1 (24.6)</td>
<td>144.9 (22.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>Anticoagulant, n (%)</td>
<td>2 (11.1)</td>
<td>10 (13.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Antiplatelet, n (%)</td>
<td>7 (38.9)</td>
<td>26 (35.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>13 (72.2)</td>
<td>34 (46.6)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiological variables</th>
<th>Parenchymal Hematoma (n=18)</th>
<th>No Parenchymal Hematoma (n=73)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DWI volume, mL (SD)</td>
<td>54.7 (75.5)</td>
<td>21.2 (22.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>VLCBV, n (%)</td>
<td>17 (94.4)</td>
<td>27 (37.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Regional reperfused-VLCBV, n (%)</td>
<td>17 (94.4)</td>
<td>19 (26)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Target mismatch profile, n (%)</td>
<td>14 (78)</td>
<td>61 (84)</td>
<td>0.7</td>
</tr>
<tr>
<td>Poor collateral flow, n (%)</td>
<td>10 (59)</td>
<td>32 (57)</td>
<td>0.9</td>
</tr>
<tr>
<td>Median mRS</td>
<td>4 (1.75–5.25)</td>
<td>3 (1–4)</td>
<td>0.07</td>
</tr>
<tr>
<td>mRS 5–6, n (%)</td>
<td>8 (44)</td>
<td>13 (18)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Poor collateral flow is defined as a score of 0–2 on a 5-point collateral scale. DWI indicates diffusion-weighted imaging; IQR, international quartile range; IV, intravenous; mRS, modified Ranking Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; and VLCBV, very low cerebral blood volume.12

$*P$ values are obtained from univariate logistic regression analyses.
The VLCBV criteria defined in this study and the test characteristics of VLCBV for predicting PH will also need to be validated. A larger data set is necessary to confirm that VLCBV improves the risk stratification compared with the sole use of a DWI lesion volume threshold. Given the increasing use of computed tomographic perfusion before endovascular therapy, future studies should further elucidate whether an analogous approach using computed tomographic perfusion can equal the performance of VLCBV based on MR perfusion. Data suggest that imaging prediction of hemorrhage using computed tomographic perfusion may require slightly different parameters.2

If the results of this study are validated, VLCBV can be used for risk stratification of patients scheduled to undergo endovascular therapy in trials and routine clinical practice. Although the modest positive predictive value precludes its use as a criterion to exclude patients from endovascular therapy, its excellent sensitivity and negative predictive value can reassure physicians and patients of the relative safety of endovascular treatment in the absence of VLCBV.
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Disclosures
Dr Christensen is a consultant for IschemaView Inc. Dr Straka is a consultant for IschemaView Inc and shareholder of iSchemaView Inc. Dr Albers is a consultant for IschemaView Inc and shareholder of iSchemaView Inc. Dr Bammer is a shareholder of iSchemaView Inc. Dr Albers, and Dr Lansberg report funding from the National Institute of Neurological Disorders and Stroke (R01 NS03932505 to Dr Albers, K23 NS051372 to Dr Lansberg, and 1Z1ANS003043 to Dr Cereda).

References
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脳血流量が非常に少ない病変の再灌流は、血管内治療後の脳実質内出血を予測する

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