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 \( (T_{\text{max}} < 6 \text{ s}) \) 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 ≥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%; \( P=0.001 \)), 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;46:00-00. 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 ≥18 years, baseline National Institute of Health Stroke Scale (NIHSS) ≥5,
nonpregnant state, premorbid modified Ranking Scale (mRS) ≤2, and no contraindication for magnetic resonance imaging (MRI).²

**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. 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]).³ 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 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 brain territory with abnormal perfusion (T<sub>max</sub> ≤ 6 s) of the baseline VLCBV lesion. Patients with regional reperfusion of their VLCBV lesion were categorized as regional reperfused-VLCBV. Reperfusion was also assessed globally by an experienced neuroendovascular radiologist (M.P.M.) on the digital subtraction angiography images by the same investigator according a predefined 5-point scale where 0 is no collateral flow and 4 is complete and rapid collateral flow to the ischemic territory.¹¹ Target mismatch pattern on baseline MRI was defined per criteria used in the parent study.³ The presence of PH (either PH1 or PH2) was assessed on the gradient recalled echo sequence of the subacute MRI.¹²–¹⁴

**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.⁴ 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).

**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 ≥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 score, 2b or 3).

Parenchymal hematoma occurred in 39% (17 of 44) of patients with VLCBV compared with 2% (1 of 47) of patients without VLCBV (P<0.0001; Figure 1). The test characteristics of VLCBV for predicting PH in the overall cohort and separately in patients with and without the target mismatch are listed in Table 2. This table also reports the hemorrhage rates and test characteristics of VLCBV in the setting of regional and global reperfusion.

Significant baseline predictors of PH in univariate analyses were the NIHSS score, DWI lesion volume, bridging with intravenous tPA, and the presence of VLCBV or regional reperfused-VLCBV (Table 3). In multivariate analysis, VLCBV remained as an independent predictor of PH (odds ratio [OR], 33; 95% confidence interval [CI], 4.0–270; P<0.001) in addition to bridging with intravenous tPA (OR, 3.8; 95% CI, 1.1–13.5; P=0.04). In a separate model, regional reperfused-VLCBV remained as the single independent predictor of PH with an OR of 53 (95% CI, 6.4–439.7440; P<0.001). In this multivariate model, bridging with intravenous tPA was removed in the backward elimination procedure because the association between this variable and PH was borderline significant (OR, 3.7; 95% CI, 0.97–14.1; P=0.056).

VLCBV was a predictor of poor functional outcome (mRS≥2) at 90 days (OR, 2.7; 95% CI, 1.1–6.2). After adjusting for age and baseline NIHSS the OR for poor functional outcome was 2.9 (95% CI, 1–8.5; P=0.05). VLCBV was also associated with a shift in the distribution of mRS toward worse functional outcome (P=0.047).

### 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 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%</td>
<td>98%</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%</td>
<td>98%</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%</td>
<td>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%</td>
<td>98%</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%</td>
<td>77%</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.

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

<table>
<thead>
<tr>
<th></th>
<th>Parenchymal Hematoma (n=18)</th>
<th>No Parenchymal Hematoma (n=73)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>Antplatelet, 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>4 (5.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>IV alteplase, n (%)</td>
<td>13 (72.2)</td>
<td>34 (46.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Radiological variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>90-d Functional outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median IQR</td>
<td>4 (1.75–5.25)</td>
<td>3 (1–4)</td>
<td>0.07</td>
</tr>
<tr>
<td>mRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 5–6, n (%)</td>
<td>8 (44)</td>
<td>13 (18)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*P values are obtained from univariate logistic regression analyses.
of VLCBV can be used to reassure physicians and patients of a very low risk of PH after endovascular treatment.

For an imaging characteristic, such as VLCBV, to be used for risk stratification, it is important to be able to assess its presence in a reliable, reproducible, and consistent manner. Automated image analysis programs can be useful in this regard. We integrated the VLCBV algorithm within an existing fully automated postprocessing software suite for perfusion imaging (RAPID). This program generated easy to interpret fully automated postprocessing software suite for perfusion imaging results of this study are in line with those of previous studies, which also report excellent sensitivity/negative predictive value and moderate to good specificity/positive predictive value for predicting PH based on VLCBV.

Our finding that specificity is improved in the presence of regional reperfusion of the VLCBV lesion is also in accordance with previous studies. In our study, patients with VLCBV developed PH exclusively in the setting of regional reperfusion (Figure 1). In addition to regional reperfusion, we evaluated the effect of global reperfusion (ie, reperfusion rated according to postprocedural modified Thrombolysis in Cerebral Infarction scores) on the association between VLCBV and PH. In the presence of global reperfusion, specificity for predicting PH increased but because of poor spatial agreement between the region of reperfusion and the VLCBV lesion, sensitivity was dramatically reduced (94%–50%). Taken together with the results of the previous studies, our results indicate that VLCBV is a predictor of PH in the setting of regional reperfusion, regardless of whether reperfusion is achieved through intravenous thrombolysis or endovascular therapy.

In addition to VLCBV, bridging with intravenous tPA was an independent predictor of PH after endovascular therapy in our study. This association could not be evaluated in previous VLCBV studies because these studies were limited to patients treated with intravenous tPA alone. The association between bridging with intravenous tPA and PH was slightly weaker in the multivariate model with reperfused-VLCBV compared with the model with VLCBV, suggesting that the effect of tPA may, in part, be mediated by tPA-induced reperfusion. However, even after adjusting for reperfused-VLCBV, our results show a trend toward an independent association between bridging with intravenous tPA and PH (P=0.06). This is a novel finding, which suggests that bridging with intravenous tPA may increase the risk of PH after endovascular reperfusion. These findings should, however, strictly be viewed as hypothesis generating and require validation in other data sets as they are in contrast with previous studies, which have not shown an association between bridging with intravenous tPA and PH or SICH after endovascular therapy.

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.

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.

Figure 2. Example of parenchymal hematoma in a patient with very low cerebral blood volume (VLCBV). A 50-year-old patient presented with a left hemispheric stroke secondary to a left middle cerebral artery occlusion. The patient’s baseline perfusion scan, processed with a fully automated VLCBV analysis program, demonstrates a 21-mL region of VLCBV in the left middle cerebral artery territory (A, shows the standard CBV map and B shows the CBV map with the VLCBV lesion segmented in purple). Complete reperfusion of this VLCBV lesion was demonstrated on follow-up imaging and a parenchymal hematoma is seen in the region corresponding to the baseline VLCBV lesion on the follow-up gradient recalled echo sequence (C).
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Disclosures

Dr Christensen is a consultant for IschemiaView Inc. Dr Straka is a consultant for IschemiaView Inc and minor shareholder of IschemiaView Inc. Dr Bammer is a shareholder of iSchemaView Inc. Dr Albers is consultant for IschemaView Inc and shareholder of iSchemaView Inc. Dr Bammer is a shareholder of iSchemaView Inc. Dr Albers is consultant for IschemaView Inc and minor shareholder of IschemaView Medical Research Council of Australia.

References

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脳血液量が非常に少ない（VLCBV）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

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

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脳血液量が非常に少ない（VLCBV）領域があることが認められた虚血性脳卒中患者では、アルテプラーゼの静脈内投与による再灌流後で脳実質内出血（PH）のリスクが増加する。本研究では、VLCBV 部を自動的に検出する方法を開発し、VLCBV 部の再灌流を達成した患者では血管内再灌流治療後に PH のリスクが増大するか否かについて検討した。

方法：受信者動作特性（ROC）分析を実施し、Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2（DEFUSE 2）試験に参加した患者の PH に関連する相対的 CBV 関値を最適化した。治療開始前の画像で相対的に CBV が低く、かつ時間登録した早期追跡調査の磁気共鳴断層撮影（MRI）で正常灌流（rT CAS < 6 秒）が認められた部位を再灌流 VLCBV 部とした。VLCBV、再灌流 VLCBV 部、および PH の関連性を、単変量および多変量解析で評価した。

結果：患者 91 例において、PH を予測する最大曲線下面積は相対 CBV 関値 < 0.42 で認められた（曲線下面積：0.77）。この閾値では、VLCBV 病変の容積 ≥ 3.55 mL が PH を最適に予測し、その感度は 94%，特異度は 63% であっ

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