Regional Very Low Cerebral Blood Volume Predicts Hemorrhagic Transformation Better Than Diffusion-Weighted Imaging Volume and Thresholded Apparent Diffusion Coefficient in Acute Ischemic Stroke

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Background and Purpose—Currently, diffusion-weighted imaging (DWI) lesion volume is the most useful magnetic resonance imaging predictor of hemorrhagic transformation (HT). Preliminary studies have suggested that very low cerebral blood volume (VLCBV) predicts HT. We compared HT prediction by VLCBV and DWI using data from the EPITHET study.

Methods—Normal-percentile CBV values were calculated from the nonstroke hemisphere. Whole-brain masks with CBV thresholds of the <0, 2.5, 5, and 10th percentiles were created. The volume of tissue with VLCBV was calculated within the acute DWI ischemic lesion. HT was graded as per ECASS criteria.

Results—HT occurred in 44 of 91 patients. Parenchymal hematoma (PH) occurred in 13 (4 symptomatic) and asymptomatic hemorrhagic infarction (HI) in 31. The median volume of VLCBV was significantly higher in cases with PH. VLCBV predicted HT better than DWI lesion volume and thresholded apparent diffusion coefficient lesion volume in receiver operating characteristic analysis and logistic regression. A cutpoint at 2 mL VLCBV with the <2.5th percentile had 100% sensitivity for PH and, in patients treated with tissue plasminogen activator, defined a population with a 43% risk of PH (95% CI, 23% to 66%, likelihood ratio=16). VLCBV remained an independent predictor of PH in multivariate analysis with traditional clinical risk factors for HT.

Conclusions—VLCBV predicted HT after thrombolysis better than did DWI or apparent diffusion coefficient volume in this large patient cohort. The advantage was greatest in patients with smaller DWI volumes. Prediction was better in patients who recanalized. If validated in an independent cohort, the addition of VLCBV to prethrombolysis decision making may reduce the incidence of HT. (Stroke. 2010;41:82-88.)

Key Words: stroke ■ thrombolytic therapy ■ hemorrhage ■ MRI

Symptomatic hemorrhagic transformation (HT) occurs in ≈2% to 8% of patients after stroke thrombolysis1–3 and is associated with an ≈45% mortality.4 Clinical risk factors for HT include increasing age, stroke severity, hypertension, and hyperglycemia or known diabetes,5 but none of these factors alone or in combination is sufficiently powerful to alter treatment decisions. Imaging predictors of HT include established hypodensity on computed tomography (CT) quantified as an ASPECTS score ≥76,7 or involvement of 1/3 of the middle cerebral artery territory. The latter is often considered a relative contraindication to administration of tissue plasminogen activator (tPA).8,9 However, very early ischemic changes on CT may be subtle, and there is poor interobserver reproducibility.10,11 Magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) is more sensitive for acute ischemia than is CT.12 Furthermore, a DWI lesion volume ≥100 mL on baseline scan is associated with a 16.1% risk of symptomatic HT (symptomatic intracerebral hemorrhage...
Cerebral blood volume (CBV) maps are derived from tracking the passage of an intravenous gadolinium bolus on perfusion-weighted imaging (PWI). Very low CBV (VLCBV) values reflect the virtual absence of gadolinium arrival in a voxel of tissue and therefore identify the most severely ischemic tissue. Other perfusion maps (eg, mean transit time, cerebral blood flow) become unreliable in the virtual absence of flow, and hence, CBV was used for this study. In a small, retrospective series of 20 patients, low CBV predicted HT better than did thresholded apparent diffusion coefficient (ADC). Therefore we used the imaging and clinical data from the EPITHET study to investigate whether VLCBV improved the prediction of HT, compared with DWI lesion volume.

Methods

EPITHET was a prospective, double-blind, multicenter trial with acute hemispheric stroke patients randomized to intravenous tPA or placebo 3 to 6 hours after symptom onset. Methodologic details have been reported previously. In brief, a baseline noncontrast CT scan was used to exclude patients with acute hemorrhage and major early ischemic change involving >1/3 of the middle cerebral artery territory (24 patients). Patients underwent MRI (including DWI, PWI, and magnetic resonance angiography [MRA]) and clinical assessment with the National Institutes of Health Stroke Scale (NIHSS) performed before treatment (acute) and repeated on day 3 to 5 (subacute) and day 90 (late) after acute stroke. Randomization to tPA or placebo was carried out without knowledge of the MRI results, which were analyzed offline to determine the presence of DWI-PWI mismatch.

Acute and subacute MRI studies were used for this analysis. The PWI source data were used to calculate CBV maps by standard techniques. These images were manually bisected through the interhemispheric fissure. A brain tissue mask with ADC values corrected for the passage of an intravenous gadolinium bolus on retrospective series of 20 patients, low CBV predicted HT of flow, and hence, CBV was used for this study. In a small, retrospective series of 20 patients, low CBV predicted HT better than did thresholded apparent diffusion coefficient (ADC). Therefore we used the imaging and clinical data from the EPITHET study to investigate whether VLCBV improved the prediction of HT, compared with DWI lesion volume.

and multivariate logistic regression was applied both for binary HT/no HT and PH/no PH outcomes as well as for the ordinal scale of no HT/PH/PH. Variables with univariate $P<0.2$ were entered into multivariate analysis. The interaction of VLCBV and recanalization was analyzed by $\chi^2$ with 2-tailed Fisher’s exact probability value.

Results

Of 100 patients enrolled in EPITHET, 91 had baseline PWI and DWI scans and follow-up imaging (MRI or CT). In the remaining nine patients, 5 had inadequate-quality baseline PWI data due to motion artifact or failed gadolinium injection, 3 patients did not have subacute imaging (due to death in 2 cases; 1 unrelated, 1 due to PH contralateral to the infarct >24 hours after tPA and contributed to intravenous heparin), and 1 patient did not have a baseline DWI or PWI lesion (pontine infarct on follow-up imaging). Forty-four of 91 patients developed HT: 13 PH (4 symptomatic) and 31 asymptomatic HI (Table 1). Figure 1 illustrates the MRI appearance of VLCBV within the DWI lesion at baseline with subsequent PH at the day 3 scan.

There were significant differences in median VLCBV volume between HT categories at all percentile thresholds tested (Table 2). The <2.5th percentile threshold (VLCBV2.5) gave optimal results, with higher VLCBV volumes in patients with HT compared with those with no HT ($P=0.0002$), in those with PH compared with those without PH ($P=0.001$), in PH compared with HI ($P=0.038$), and in HI compared with no HT ($P=0.007$). Volumes of DWI and ADC <550 were also higher in HT compared with no HT and PH compared with no PH (Figure 2).

In the ROC analysis, VLCBV had a nonsignificantly higher area under the curve (AUC) than did DWI lesion volume at all percentile thresholds tested (online Table). The optimal AUC was at the <2.5th percentile, and this became significantly better than DWI in the subgroup with recanalization/patent vessel at outcome (Figure 3). VLCBV2.5 was therefore used for subsequent analysis.

Absolute ADC thresholds were better at distinguishing infarcted from normal tissue than were relative thresholds but still included significant false-positive voxels in the normal hemisphere. Thresholds of $550 \times 10^{-6} \text{mm}^2\text{s}^{-1}$ have been used previously to identify the ischemic core, and higher thresholds had >15% nonspecific “low ADC” in the mirror ROI. In the ROC analysis, ADC <550 with 2-tailed Fisher’s exact probability value.

Logistic regression was applied after transformation to normalize the data (Table 3). For the binary PH versus no PH analysis, VLCBV2.5, ADC <550, and DWI were significant in univariate analysis. These variables were highly correlated (DWI-VLCBV2.5 $R=0.86$, DWI-ADC <550, $R=0.90$). The probability value for VLCBV2.5 ($P=0.007$) was superior to that for DWI ($P=0.023$) and ADC <550 ($P=0.026$). Atrial fibrillation (AF) was the only significant univariate clinical predictor of PH ($P=0.009$). In multivariate analysis with AF and tPA, VLCBV2.5 ($P=0.014$), DWI ($P=0.035$), and ADC <550 ($P=0.022$) all remained significant. However, addition of DWI or ADC <550 to VLCBV2.5 did not improve the model. The same pattern was seen with the binary HT versus PH model.
no HT outcome (VLCBV2.5 P=0.0004, DWI P=0.001, ADC <550, P=0.002).

Ordinal logistic regression was then applied with no HT, HI, and PH as sequentially more severe degrees of HT. No weighting is implied by this method. Increasing VLCBV2.5, ADC <550, and DWI volumes were again all significant predictors of HT used alone, but the probability value and Cox-Snell pseudo-$R^2$ for the VLCBV2.5 model were superior (VLCBV2.5 $P=0.00001$, $R^2=0.20$; ADC $<550 P=0.0002$, $R^2=0.14$; DWI $P=0.0001$, $R^2=0.15$). All 3 parameters remained significant when the effects of diabetes, AF, and baseline NIHSS score were factored into multivariate analysis (VLCBV2.5 $P=0.00001$, $R^2=0.29$; ADC $<550 P=0.0002$, $R^2=0.27$; DWI $P=0.0007$, $R^2=0.26$). In the model combining DWI, ADC $<550$, and VLCBV with baseline NIHSS score, AF, and diabetes, we found that AF ($P=0.005$), diabetes (0.045), and VLCBV2.5 ($P=0.045$) remained significant, but DWI ($P=0.439$) and ADC $<550$ ($P=0.20$) did not.

Recanalization status was known in 77 cases. Baseline vessel occlusion was present in 47, and 23 had recanalized by day 3 to 5. Therefore, 53 had a patent vessel at day 3 to 5, and all 8 PH cases occurred in this group (5 recanalized, 3 no recanalization). Baseline NIHSS score was 74±10 in this group (5 recanalized, 3 no recanalization). In the EPITHET cohort, 46 of 91 cases had VLCBV2.5 $\geq$2 mL. Of these, 13 (28%) had PH, and only 5 (11%) achieved a modified Rankin Scale score (mRS) of 0 to 1 at day 90. Of the VLCBV2.5 $>2$-mL patients, 21 of 46 received tPA, and the risk of PH in these patients was 43% (95% CI, 22% to 66%; LR=16, $P=0.0003$). Recanalization status was known in 8 of 13 PH cases, all of whom had a patent vessel by day 3 to 5. The frequency of PH in patients with recanalization and baseline VLCBV2.5 $>2$ mL was 50% (95% CI, 19% to 81%; LR=10, $P=0.007$) and in patients with a patent vessel at day 3 to 5 and a baseline VLCBV2.5 $>2$ mL, it was 35% (95% CI, 16% to 57%; LR=15, $P=0.001$). The smallest DWI lesion with $>2$ mL VLCBV2.5 was 8.8 mL, and the largest DWI lesion with $<2$ mL VLCBV2.5 was 45.7 mL. The variability in the VLCBV-DWI relation therefore arose in the range of $\sim10$ to 50 mL DWI volume. All stroke patients with $>50$ mL DWI (21% of the entire cohort) had significant VLCBV. None of these patients achieved an mRS of 0 to 1 at day 90, and 58% had an mRS of 5 to 6.

If the $>2$ mL VLCBV2.5 criterion were used to exclude patients from thrombolysis, $\sim50\%$ of patients in the 3- to 6-hour window might be excluded from receiving tPA. The frequency of DWI-PWI mismatch was reasonably evenly distributed between groups. The exclusion of patients with $>100$ mL DWI lesions would have excluded 12 patients but encompassed only 3 of the 14 PH cases: sensitivity=21%, specificity=88%. If, however, the VLCBV2.5 $>2$ mL criterion is applied after exclusion of cases with a DWI lesion $>100$ mL, then the specificity of VLCBV for PH in tPA-treated patients improves from 67% to 75% with a positive predictive value=0.47 and LR=16.

### Discussion

This study has demonstrated that VLCBV is a strong predictor of the risk of HT. Increasing volumes of VLCBV are associated with increasing risk of PH, and all PH cases were predicted with a VLCBV2.5 cutpoint of $>2$ mL. Recanaliza-
tion of baseline vessel obstruction appears to be a prerequisite for development of PH. This makes intuitive sense, because even if the vasculature is severely damaged within a region of infarct, a PH will only eventuate if blood flow is restored. Four patients not treated with tPA developed PH. All 3 with MRA data had a combination of significant VLCBV and spontaneous recanalization. This illustrates the central role of recanalization rather than tPA per se in PH and has implications for intra-arterial clot retrieval, given the likelihood of increased recanalization rates with these techniques.

The PH risk of 28% with >2 mL VLCBV2.5 observed in the entire cohort is an underestimate of the true magnitude of the VLCBV-PH relation, owing to “dilution” by cases without recanalization. Only half of the patients received tPA, and not all of them recanlized. Within these subgroups, the PH risk associated with a >2-mL VLCBV2.5 increased to 43% and 50%, respectively. Ideally, reperfusion would be assessed, as not all patients who recanalize actually reperfuse the tissue affected by the VLCBV. However, technical limitations due to the susceptibility artifact caused by PH prevented this analysis. Although recanalization or reperfusion cannot be known at baseline, treatment with tPA or intra-arterial techniques implies an intention to achieve reperfusion, and therefore, risk estimation should be based on this premise.

These data confirm previous work that the relative risk of PH increases with larger DWI lesion volume.13 However, the majority of PHs in absolute terms occur in relatively small strokes, such that excluding high-DWI-volume strokes (eg, >100 mL) from treatment lacks sensitivity for PH. Furthermore, using a lower DWI threshold chosen to have high sensitivity for PH yields very poor specificity (40%) and would exclude the majority of patients from treatment. VLCBV has better specificity at high sensitivity levels, a differential that is enhanced by exclusion of patients with very large DWI lesions. We speculate that these large DWI lesions are associated with more proximal arterial occlusions and therefore, higher clot burden. As a result, intravenous tPA would be expected to result in lower reperfusion rates, thus confounding the usual VLCBV-PH relation and lowering apparent specificity.

The overall advantage of VLCBV over DWI is consistent with the hypothesized direct relation of VLCBV to the severe ischemia required to cause HT by damaging blood vessel integrity. In contrast, DWI/ADC changes are a downstream effect of ischemia on neurons that may occur with less severe ischemia. Although lower ADC values have been observed in the more severely damaged infarct core,19 thresholded ADC did not improve HT prediction compared with DWI lesion volume. This is compatible with the hypothesis that the level of ischemia leading to neuronal death (and ADC/DWI

| Table 2. DWI, ADC, and VLCBV Volumes by HT Category |
|-------------------------------|----------------|----------------|
| Median Volume, mL             | DWI            | ADC<550        |
| No HT                         | 12.7           | 3.55           |
| HI                            | 26.1           | 11.2           |
| PH                            | 52.5           | 11.7           |

P values (Mann-Whitney U test)

<table>
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<tr>
<th></th>
<th>No HT vs any HT</th>
<th>HI vs no HT</th>
<th>HI vs PH</th>
<th>PH vs no PH</th>
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<td>0.0002</td>
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<td>0.001</td>
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<td>0.06</td>
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Figure 1. A 64-year-old woman with baseline VLCBV, who achieved recanalization and reperfusion, and developed PH after tPA. A, CBV map. VLCBV2.5 (region of virtually no contrast arrival) shown in red with DWI lesion ROI outlined in green. B, Gradient-echo image demonstrating PH at follow-up on day 3. C, Acute Tmax map demonstrating large area of hypoperfusion. D, Day 3 Tmax map demonstrating reperfusion. E, Acute MRA showing M1 occlusion at 3.25 hours. F, Day 3 MRA showing recanalization.
changes) is less severe than that required to damage blood vessel integrity, represented by VLCBV.

The absence of gadolinium contrast arrival in tissue indicated by VLCBV results from the combination of vessel occlusion and inadequate collateral circulation. The presence of collaterals varies significantly between individuals, but generally there are 2 circumstances under which VLCBV can occur. In large infarcts, it is unlikely that collaterals will be able to supply the entire area. This was indicated by the universal presence of >2-mL VLCBV in patients with a DWI lesion volume >50 mL, a population with generally poor outcome. The second situation occurs when the occlusion affects an end vessel, such as a cortical branch or lenticulostriate perforator, where there is no possibility of a collateral supply. This scenario leads to significant VLCBV (and attendant risk of PH) despite a relatively small DWI lesion, which underlies the inferior performance of DWI as a predictor of PH.

The calculation of VLCBV is relatively straightforward. It could potentially be automated and occur simultaneously in software designed for automated penumbral selection. In this way, VLCBV could be used to predict the risk of PH, should reperfusion occur. The method appears robust. The EPITHET data were collected from 15 centers with different MRI scanners, so the analysis is not limited to any particular manufacturer or proprietary software. The use of a very low-percentile threshold equating to virtually no gadolinium arrival is not affected by the relative nature of CBV values derived from MRI.

Whether a 43% risk of PH should justify excluding ~50% of eligible patients from treatment after other exclusions, such as >1/3 middle cerebral artery early ischemic change, is as yet uncertain. Although PH may not be symptomatic by the common definition of an increase of ≥4 NIHSS points, outcome after PH is usually poor (PH2 had 60% 90-day mortality in the tPA meta-analysis, and in EPITHET, only 2 of 15 PH patients achieved an mRS of 0 to 1). Whether PH is symptomatic is related to lesion location and volume, rather than any fundamental difference in pathophysiology. In contrast, with the exception of 1 study that suggested an association between HI and poorer long-term outcome, HI is generally regarded as a benign epiphenomenon of no

Figure 2. Box-and-whisker plot of transformed VLCBV2.5 (A), DWI (B), and ADC < 550 volume (C) (mL^0.2) by HT category.

Figure 3. ROC analysis for DWI and VLCBV2.5 volume predicting PH. A, Entire cohort (N=91). B, Patent vessel at follow-up (n=53). C, Recanalization (n=23). The predictive power of VLCBV2.5 is improved by vessel patency/recanalization, and VLCBV2.5 becomes significantly better than DWI.
clinical consequence. Despite this, some studies have classified a proportion of patients with HI as having SICH, reflecting the difficulties of attributing the cause of clinical deterioration in acute stroke. Depending on the definition used, SICH is also relatively uncommon, which, combined with the imprecision in classification, limits its statistical power as an end point. For all of these reasons, we believe that PH is a more appropriate adverse end point than SICH.

The main limitation of this study is the post hoc nature of the 2-mL VLCBV cutpoint. This requires validation in an independent dataset. There are also insufficient data on recanalization in this cohort to perform sophisticated statistical analysis of the interaction with VLCBV, although this does appear relatively clear-cut. This study purely examined data from the 3- to 6-hour treatment window, and further study in the 0- to 3-hour time frame will be needed to assess the association of VLCBV with PH risk in patients treated earlier.

It seems likely from our results that calculation of VLCBV could improve patient selection for acute reperfusion therapy. Recanalization (as a surrogate for reperfusion) is a prerequisite for the development of PH and, together with the presence of >2-mL VLCBV2.5, defines a very high-risk group. If further validated, VLCBV could be incorporated in clinical decision making to balance the risk of HT against the potential benefits of reperfusion in patients, as judged by the volume and location of potentially salvageable penumbral tissue. Patients with a high VLCBV would be an ideal target population for trials of putative neuroprotective agents that may reduce the risk of HT.

Table 3. Logistic-Regression Analysis

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>HT vs no HT</th>
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<th></th>
<th>PH vs no PH</th>
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<th>Ordinal logistic‡</th>
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<tbody>
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<td></td>
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<td>Multivariate</td>
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<td>Univariate</td>
<td>Multivariate</td>
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<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P Value</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P Value</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P Value</td>
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<td>Age (per decade)</td>
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<tr>
<td>Baseline NIHSS (per unit)</td>
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<td>1.02</td>
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<td>3.71</td>
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<td>AF</td>
<td>2.58</td>
<td>1.09–6.11</td>
<td>0.031</td>
<td>2.20</td>
<td>0.82–5.93</td>
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<td>tPA</td>
<td>0.875</td>
<td>0.38–1.99</td>
<td>0.750</td>
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<td>DWI volume (mL⁻⁰.⁵)</td>
<td>15.0</td>
<td>2.90–77.5</td>
<td>0.001</td>
<td>14.6*</td>
<td>2.23–95.2</td>
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<tr>
<td>ADC &lt;550 (mL⁻⁰.⁵)</td>
<td>5.51</td>
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<td>0.002</td>
<td>5.18*</td>
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<td>VLCBV2.5 (mL⁻⁰.²)</td>
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<tr>
<td>Baseline NIHSS (per unit)</td>
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<tr>
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<tr>
<td>DWI volume (mL⁻⁰.⁵)</td>
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<tr>
<td>ADC &lt;550 (mL⁻⁰.⁵)</td>
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<td>1.19–17.2</td>
<td>0.026</td>
<td>6.16†</td>
<td>1.30–29.2</td>
<td>0.022</td>
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<tr>
<td>VLCBV2.5 (mL⁻⁰.²)</td>
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<td>1.52–13.4</td>
<td>0.007</td>
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*Odds ratio was adjusted for diabetes, AF, and baseline NIHSS score.
†Odds ratio was adjusted for AF and tPA.
‡For 3 HT categories: no HT, HI, and PH and a complementary log-log link function. All odds ratios were arranged so that an odds ratio >1 indicates increased risk of HT.
§Odds ratio was adjusted for diabetes, AF, and baseline NIHSS score.

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