Low Cerebral Blood Volume Is Predictive of Diffusion Restriction Only in Hyperacute Stroke

Michael Knash, MD; Adrian Tsang, BASc; Bilal Hameed, MD; Monica Saini, MD; Thomas Jeerakathil, MD, MSc; Christian Beaulieu, PhD; Derek Emery, MD, MSc; Kenneth Butcher, MD, PhD

**Background and Purpose**—Diffusion-weighted MRI (DWI) demonstrates ischemic tissue with high sensitivity. Although low cerebral blood volume (CBV) is also used as a marker for infarction, the quantitative relationship between diffusion abnormalities and CBV is unknown. We tested the hypothesis that CBV would decrease proportionally to the apparent diffusion coefficient in patients with acute stroke and thus could be used as a surrogate parameter for diffusion restriction.

**Methods**—Perfusion-weighted imaging and DWI was performed in 54 patients within 28 hours of symptom onset. Mean apparent diffusion coefficient, cerebral blood flow, and CBV were measured within DWI lesions and contralateral regions.

**Results**—Within DWI lesions, CBV (3.3±1.9 mL/100 g) was significantly decreased relative to contralateral regions (4.1±2.1 mL/100 g, P<0.001). Relative CBV was not decreased in patients with evidence of early reperfusion (1.2±0.5) or mild stroke (National Institutes of Health Stroke Scale <4, 1.1±0.6). Linear regression indicated that relative CBV was predictive of relative apparent diffusion coefficient only in patients imaged within 9 hours of symptom onset (R=0.50, P=0.02). Ischemic tissue volumes generated using a CBV threshold of the 50th percentile of normal tissue were correlated with DWI lesion volumes (R=0.73, P<0.001). The mean difference between the CBV threshold of the 50th percentile of normal tissue and DWI lesion volumes was 6.3 mL (95% limits of agreement, 0.1 to 12.6 mL).

**Conclusions**—Decreases in relative CBV are predictive of diffusion abnormalities in ischemic stroke. The pattern of CBV changes varies with clinical severity and symptom duration. Ischemic tissue volumes comparable to DWI lesions can be generated using CBV thresholds, but the use of this method is limited in patients with minor stroke. *(Stroke. 2010;41:2795-2800.)*

**Key Words:** acute stroke • cerebral hemodynamics • diffusion-weighted MRI

Diffusion (DWI) and perfusion-weighted (PWI) MRI are highly sensitive for acute ischemic changes. DWI identifies regions of bioenergetic compromise,1–3 whereas PWI provides cerebral blood flow and volume data. Although acute diffusion restriction does not predict infarction with perfect specificity, DWI lesions in most cases represent irreversibly injured tissue.4–6 Mismatch between a smaller volume of compromised tissue visualized with DWI and larger perfusion deficit demonstrated by PWI can be used as an operational definition of the ischemic penumbra.7 Although this hypothesis remains unproven, mismatch does appear to predict treatment response.

In many centers, access issues have limited the use of MRI in acute stroke. Increasingly, CT perfusion (CTP) is being used in lieu of MRI. Unlike MRI, CTP does not provide a direct marker of bioenergetic failure. However, cerebral blood volume (CBV) maps may provide an alternative marker of tissue irreversibly destined for infarction. Under ischemic conditions, as cerebral perfusion pressure falls, an initial homeostatic response is vasodilatation, facilitating increased oxygen extraction and also resulting in an increase in CBV. In tissue where vasodilatation is insufficient to maintain tissue perfusion, CBV will fall. Decreased CBV is associated with irreversible injury and ultimately infarction.8 Thus, low CBV may be used as a surrogate for diffusion restriction in acute stroke.

Although CBV thresholds for infarction have been identified, the precise relationship between diffusion changes and CBV is unknown.9 CBV measurements are used as a surrogate for irreversible tissue injury in many centers despite a lack of systematic studies comparing CBV with other measures of bioenergetic compromise (ie, DWI). We therefore undertook a comparative MRI study examining the relationship between CBV and diffusion characteristics in patients.
with acute stroke. We aimed to identify relative CBV thresholds for diffusion restriction. We also tested the hypothesis that the apparent diffusion coefficient (ADC) and CBV within ischemic regions are directly correlated.

Methods

Subjects
All patients were part of an ongoing study of the use of DWI and PWI in ischemic stroke. The current study was a retrospective evaluation of this database. The protocol was approved by the local Human Research Ethics Board and informed consent was obtained in all cases. Eligible patients had ischemic stroke diagnosed by a stroke neurologist, were >18 years old, and had no contraindications to MRI. Patients all had visible DWI lesions on the acute scan.

Imaging Protocol
All patients were imaged with DWI and PWI using an 8-channel phased array radiofrequency head coil (MIRI Devices, Waukesha, Wisc) on a 1.5-T whole-body Siemens Sonata MRI scanner (Siemens Medical Systems, Erlangen, Germany). DWI was acquired with single-shot spin-echo diffusion echoplanar imaging, 220-mm field of view, 19.5-mm axial slices with a 1.5-mm gap, b value of 1000 s/mm² along 3 orthogonal directions, repetition time/echo time 1630/50 msec, GRAPPA R=2, and matrix size of 128×128 zero-filled to 256×256. PWI images were obtained at 60 time points per slice using single-shot gradient-echo echoplanar imaging with intravenous injection of Magnevist (Bayer HealthCare Pharmaceuticals), Gd-DTPA, at the rate of 5 mL/s, 13 to 19 5-mm axial slices with a 1.5-mm gap, repetition time/echo time 1320/50 msec, and matrix size and slice orientation identical to DWI. Axial turbo spin-echo T1- and T2-weighted images were acquired; 19 slices, repetition time/echo time 680/17 msec (T1-weighted), 5800/99 msec (T2-weighted), matrix size of 128×256 (T1-weighted), 204×256 (T2-weighted), and field of view and slice orientation identical to DWI. Fluid-attenuated inversion recovery, gradient-echo, and time-of-flight angiography images were also acquired as part of the 20-minute stroke protocol.

Image Processing
Postprocessing of raw images was performed by a single investigator (M.E.K.). Perfusion DICOM files were imported into custom Matlab 7.4 (The Mathworks) software (PGUI Perfusion Analysis Software, CFIN Aarhus University Hospital, 2007). Maps of time to peak of the tissue response were generated. An arterial input function was manually selected from the middle cerebral artery contralateral to the DWI lesion and used to calculate deconvolved maps of cerebral blood flow (CBF) and CBV.10–12 PWI and DWI images were coregistered using statistical parametric mapping (SPM8b; Wellcome Trust Centre for Neuroimaging, London, UK).

Region of Interest Analysis
Coregistered images were imported into Analyze 8.1 for region of interest (ROI) analysis.13 The DWI lesion was defined using a semiautomated threshold intensity technique. Mirrored ROIs were manually drawn over contralateral homologous regions. Mean ADC values were measured within each ROI. Voxels with ADC >120×10⁻³ mm²/s were considered to contain cerebrospinal fluid and were excluded.6,14 Relative (r) ADC was calculated as the ratio of ipsilateral to contralateral values.

Normal white matter within the contralateral centrum semiovale on CBV and CBF maps was normalized to 2 mL/100 g and 22 mL/100 g/min, respectively.15,16 Voxels with CBV >8 mL/100 g or CBF >100 mL/100 g/min were assumed to contain blood vessels and removed from the ROIs.15 Relative CBF and CBV were calculated as the ratio of CBF or CBV within the DWI lesion to that of contralateral homologous regions. Perfusion status at the time of MRI was assessed using rCBF. An rCBF >0.8 (ie, blood flow within the DWI lesion at least 80% of normal) was deemed to represent reperfusion.

T1-weighted images acquired in all patients were segmented using a tissue probabilistic map of gray (GM) and white matter (WM) included in SPM8b. The DWI ROIs, and contralateral homologous regions, were then subdivided into GM and WM regions. All ROIs were transferred to coregistered PWI maps to calculate mean absolute and rCBF and CBV values within the ischemic lesions.18 Ischemic regions were also defined using CBV thresholds based on percentiles of normal contralateral tissue. Manually drawn ROIs of all visually apparent abnormal regions seen on time-to-peak maps were superimposed on CBV maps. Within each patient, normal CBV was calculated as that of the mean of the contralateral hemisphere. CBV values corresponding to cut points of the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of these normal values were then calculated. These percentile values were then used to measure CBV-defined tissue infarct volumes within the oligemic region identified on time-to-peak maps.

Statistical Analysis
Statistical analysis was performed using SPSS 17.0. Linear regression was used to assess the relationship between ADC and CBV. Paired t tests were used to compare DWI and PWI measures between the ischemic and unaffected hemispheres. Given the heterogeneous composition of the patient population, a number of a priori-defined groups was analyzed. Patients were analyzed with respect to time between symptom onset and MRI (<9 hours versus >9 hours), stroke severity (National Institutes of Health Stroke Scale <4 versus ≥4), and perfusion status (rCBF >0.8 versus <0.8). One-way analysis of variance and post hoc Tukey tests were used to compare DWI and PWI measures between patients in these groups. The limits of agreement between ADC- and CBV-defined ischemic volumes were calculated and illustrated using Bland-Altman plots.

Results

Baseline Clinical Data
There were 103 patients with acute ischemic stroke enrolled. Fourteen patients were excluded due to an absence of DWI changes. Another 35 patients were excluded due to absent or uninterpretable PWI data. A total of 54 patients were included in the final analysis (36 males and 18 females; age 71.1±12.1; age range, 41 to 93 years). The median National Institutes of Health Stroke Scale was 6 (range, 0 to 27). Sixteen patients (30%) had minor stroke (National Institutes of Health Stroke Scale <4). The median time to MRI was 13 hours (range, 0.5 to 28 hours) and 21 patients (39%) were scanned within 9 hours of symptom onset. Twenty-two patients (41%) showed evidence of reperfusion at the time of MRI, whereas 32 had persisting hypoperfusion.

CBV Within DWI Lesions
Within DWI lesions, mean CBV in all patients was 3.3±1.9 mL/100 g and 4.1±2.1 mL/100 g (P<0.001) in contralateral regions. A number of CBV patterns were evident (Figure 1). In patients with major stroke (National Institutes of Health Stroke Scale ≥4), mean CBV was significantly lower in areas of diffusion restriction (2.88±1.43 mL/100 g, n=38) relative to contralateral homologous regions (3.2±1.14 mL/100 g, P<0.001). This pattern was not seen in patients with clinically minor stroke (National Institutes of Health Stroke Scale <4), in which mean CBV was not reduced in ischemic regions (3.48±1.61 versus 3.43±1.72 mL/100 g, P=0.84, n=16). Mean DWI lesion volume in patients with minor
stroke (6.7±7.3 mL) was significantly smaller than in patients with major stroke (17.7±2.9 mL, P=0.018).

Perfusion Effects
Mean rCBV within the DWI lesions was significantly lower in patients with persisting hypoperfusion (0.79±0.26, n=32) than in those with reperfusion (1.16±0.52, n=22, P=0.029). An elevation of CBV (rCBV >1.0) was seen in 15 of 22 (68%) of reperfused patients and only 4 of 32 (13%) of those with persisting hypoperfusion. In contrast, rADC was decreased in all patients, although it was lower in those with persisting hypoperfusion (0.69±0.09) than those with reperfusion (0.79±0.10, P=0.001).

Effect of Time Between Symptom Onset and MRI
The relationship between ADC and CBV was assessed with linear regression. There was not a significant relationship between rCBV and rADC (R=0.20, P=0.30) when all patients were assessed together. Similarly when GM and WM ADC and CBV were assessed separately, no significant relationship was found (GM: R=0.28; P=0.087; WM: R=0.04; P=0.77). Only in patients imaged <9 hours after symptom onset (n=21) was there a significant relationship between rADC and rCBV (R=0.50, P=0.02; Figure 2). Within the <9-hour group, this relationship remained significant in GM (R=0.51, P=0.025; 95% CI, 0.022 to 0.295; n=19, 2 patients had only WM lesions). The relationship was not significant in WM (R=0.42, P=0.056; 95% CI, −0.002 to 0.168; Figure 3). In patients imaged >9 hours after onset, there was no longer a relationship between rADC and rCBV (R=0.05, P=0.81).

No significant relationship between rCBV and rADC was demonstrated in minor (R=−0.01, P=0.85) or major stroke groups (R=0.04, P=0.49). In addition, no clear relationship between rCBV and rADC was found in patients with persisting hypoperfusion (R=0.09, P=0.63) or those who were reperfused at the time of scanning (R=0.06, P=0.78).

Low CBV-Defined Ischemic Lesions
Visible time-to-peak deficits were present in 46 patients. The lesion volumes defined by low CBV in these patients were significantly correlated with DWI lesion volumes (Table 1). The mean differences with 95% limits of agreement between DWI and CBV-defined ischemic lesion volumes ranged from −1.8 (−1.7 mL; 5th CBV percentile) to 40.3 (24.6, 56.0 mL; 95th percentile). Low CBV cut points tended to underestimate DWI lesion volumes (Table 2). Agreement was reasonable at the 50th percentile CBV cut point, which resulted in a mean overestimation of ADC lesion volume by 6.3 (0.1, 12.6) mL (Figure 4). At all CBV percentile cut points there was a tendency in small infarcts for CBV-defined lesion volumes to overestimate DWI volumes. Conversely, CBV-defined volumes underestimated ADC volumes in larger infarcts.

Discussion
This study confirms that low CBV is correlated with diffusion restriction in patients with acute stroke. With increasing time from symptom onset, however, the relationship between ADC and CBV becomes uncoupled. Smaller lesions visible on DWI, particularly those restricted to WM, may not be evident on CBV maps. These findings are relevant to future studies in which CBV is used as a surrogate for DWI changes.

Physiological Significance of CBV Changes
The patterns of CBV changes in the 54 patients with acute stroke studied were extremely variable. The majority of patients demonstrated decreased CBV within bioenergetically compromised tissue, as demonstrated by DWI. The largest decreases were seen in patients with more severe clinical
deficits. Many patients with DWI lesions had no corresponding regions of depressed CBV. This discordance between CBV and ADC changes appears to be related to 3 factors: stroke severity, tissue type, and time from onset.

Patients with milder clinical syndromes had smaller DWI lesions. In many of these patients, a corollary lesion was not evident on CBV maps (Figure 1). Thus, CBV appears to be a less sensitive marker for ischemic injury. It is possible that CBV normalized after reperfusion in these cases. Alternatively, many of these milder strokes were restricted to WM, where the relationship between ADC and CBV is not apparent.

There is only 1 other published comparison of ADC and CBV,19 which included only 13 patients, all of whom had large cortical infarcts imaged within 3 hours of symptom onset. The authors reported strong correlations between the volume of tissue with decreased CBV, calculated by both PWI and CTP techniques. In our larger, more heterogeneous population, we have demonstrated that the relationship between CBV and ADC is less predictable.

Normalization or elevation of rCBF within the DWI lesion indicated that reperfusion had occurred in a number of patients by the time of the MRI scan (Figure 1). This reperfusion is nonnutritive and is not associated with tissue salvage, because infarction has already occurred.20 During an acute cerebrovascular syndrome, perfusion is a dynamic process. Spontaneous reperfusion is more likely to be seen with longer intervals between symptom onset and PWI acquisition. In contrast to PWI changes, ADC is an “all-or-none” phenomenon. The ADC within oligemic areas decreases once an ischemic threshold is reached and with few exceptions1,21,22 does not normalize irrespective of perfusion changes. This is not the case with perfusion and the resulting dissociation between ADC and CBV becomes more evident with increasing duration of symptoms.

### CBV Versus ADC in GM and WM

When GM and WM were assessed independently, rADC was significantly correlated with rCBV only in GM. This may be

#### Table 1. Correlation Between ADC-Defined and CBV Percentile-Defined Lesion Volumes

<table>
<thead>
<tr>
<th>ADC Lesion Volume, mL</th>
<th>CBV Percentile 5th</th>
<th>CBV Lesion Volume, mL</th>
<th>CBV SD</th>
<th>Regression Coefficient (R)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.4 ± 34.9</td>
<td>7.14</td>
<td>13.8</td>
<td>0.85</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>10th</td>
<td>7.9</td>
<td>14.7</td>
<td>0.73</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>25th</td>
<td>13.3</td>
<td>18.9</td>
<td>0.76</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>50th</td>
<td>24.6</td>
<td>27.5</td>
<td>0.73</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>75th</td>
<td>42.1</td>
<td>44.4</td>
<td>0.67</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>90th</td>
<td>54.2</td>
<td>57.6</td>
<td>0.64</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>95th</td>
<td>58.5</td>
<td>62.9</td>
<td>0.63</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
related to the fact that GM is associated with higher infarction thresholds than WM. In addition, CBV in normal WM is already lower than that in GM, making any relative decreases less apparent.

CBV Thresholds for Diffusion Restriction

We attempted to identify CBV thresholds, based on percentile ranks of normal tissue, predictive of DWI lesion volumes. Although a CBV 50th percentile-defined lesion volume was on average predictive of areas of ADC restriction, there was a significant amount of variability between patients. Thus, identification of 1 CBV threshold reliably indicating infarct core was problematic. It is unlikely that any 1 CBV threshold for DWI changes will be identified. It has already been demonstrated using CTP that the absolute CBV threshold for infarction does vary between patients.

Limitations

The current study has several limitations. Like in all ROI-based studies, our results are complicated by lesion heterogeneity. Both ADC and CBV may vary within a single ROI. Thus, mean values within our DWI-defined lesions may not reflect the true relationship between ADC and CBV within individual voxels. In addition, because PWI acquisition is based on nondiffusible tracer kinetics, low-flow states such as in the ischemic core may result in erroneous CBV estimates. To ensure we captured the entire rise and fall of contrast tissue concentration curves, we acquired data over a 98-second scan time. Any scan displaying a tissue concentration curve not returning to baseline was excluded from analysis. MRI data were only obtained at 1 time point. Multiple PWI acquisition times are required to accurately characterize the temporal pattern of changes in CBV and ADC after stroke. Finally, because CTP-derived CBV is often used clinically as a surrogate for DWI restriction when MRI is not immediately available, the current study should be repeated using contemporaneous MRI and CTP.

Conclusions

Decreases in rCBV are predictive of diffusion abnormalities in acute ischemic stroke. The pattern of CBV changes varies with clinical severity and symptom duration. Our findings support the continued use of thresholded CBV maps as a surrogate for ischemic injury when DWI is unavailable. In patients presenting with a delay from symptom onset, however, normalization of CBV may result in underestimation of the extent of irreversibly injured tissue.

Sources of Funding

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Disclosures

None.

References


Table 2. Volumetric Discrepancies Between DWI and Low CBV-Defined Ischemic Lesions at Each CBV Percentile Cut Point

<table>
<thead>
<tr>
<th>CBV Percentile</th>
<th>ADC–CBV Mean Volume, mL</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th</td>
<td>−11.8</td>
<td>−21.9</td>
<td>−1.7</td>
</tr>
<tr>
<td>10th</td>
<td>−11.8</td>
<td>−19.6</td>
<td>−3.9</td>
</tr>
<tr>
<td>25th</td>
<td>−5.3</td>
<td>−11.6</td>
<td>1</td>
</tr>
<tr>
<td>50th</td>
<td>6.3</td>
<td>0.1</td>
<td>12.6</td>
</tr>
<tr>
<td>75th</td>
<td>19.6</td>
<td>9.3</td>
<td>29.8</td>
</tr>
<tr>
<td>90th</td>
<td>35.9</td>
<td>21.8</td>
<td>50</td>
</tr>
<tr>
<td>95th</td>
<td>40.3</td>
<td>24.6</td>
<td>56</td>
</tr>
</tbody>
</table>

Figure 4. Bland-Altman plot illustrating differences between ADC and CBV (50th percentile of normal tissue) lesion volumes. In patients with smaller infarcts, CBV tended to overestimate lesion volumes measured on diffusion images (ADC).


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低脑血容量预测脑梗死超急性期的弥散受限

Low Cerebral Blood Volume Is Predictive of Diffusion Restriction Only in Hyperacute Stroke

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背景与目的：弥散加权 MRI (Diffusion-weighted MRI, DWI) 对缺血组织具有高度敏感性。尽管低脑血容量 (cerebral blood volume, CBV) 也可用作脑梗死的标识,但它与弥散异常的定量关系尚未建立。我们验证了假说: 在急性脑梗死患者, CBV 的降低与表观弥散系数的改变成比例关系, 故可用作弥散受限的替代指标。

方法：在 54 名发病 28 小时内的脑梗死患者进行灌注加权成像和 DWI, 在 DWI 病灶和对侧相应区域内进行平均表观弥散系数、脑血流量和 CBV 的测量。

结果：在 DWI 病灶内, CBV 较对侧显著性降低 (3.3±1.9 mL/100 g 和 4.1±2.1 mL/100 g, P<0.001), 但相对 CBV 在早期再灌注和 NIHSS 评分 <4 分的轻卒中患者并无显著变化 (1.2±0.5 和 1.1±0.6)。线性回归显示相对 CBV 只适于发病 9 小时以内的患者作相对表观弥散系数的预测 (R=0.50, P=0.02)。采用正常脑组织 CBV 的 50% 作为阈值所检测的缺血组织体积与 DWI 病灶体积具有显著相关性 (R=0.73, P<0.001), 两种方法测得病灶体积的平均差别为 6.3 mL (95% 可信区间为 0.1-12.6 mL)。

结论：相对 CBV 的降低能够预测急性脑梗死的弥散异常。CBV 的改变模式随着临床症状的严重程度和持续时间而变化。采用 CBV 阈值所检测的缺血组织体积与 DWI 病灶体积相似, 但是该方法不适用于轻型卒中患者。

关键词：急性脑梗死, 脑血流动力学, 弥散加权 MRI

(Stroke. 2010; 41:2795-2800. 中山大学附属第一医院神经内科 廖松洁 译 曾进胜 校)
激发梯度回波横断面扫描,层厚显,功能,用于计算脑血流侧相应区域。将灌注CBV\(^{[10–12]}\)和联合登记。

London, UK) (SPM8b; Well-come Trust Centre for Neuroimaging,感兴趣区域分析

研究方案已获得当地人类试验伦理委员会的批准,并签署了知情同意书。纳入了由神经科医生诊断为脑梗死的患者, 年龄 18 岁以上, 无 MRI 禁忌症, 有急性期 DWI 病灶。

成像方法

所有患者接受了 DWI 和 PWI, 采用 1.5T Siemens Sonata MR 扫描仪 (Siemens Medical Systems, Erlangen, 德国) 和 8 通道相位排列的射频螺旋头 (MRI Devices, Waukesha, Wisc)。DWI 采用单次激发自旋回波弥散横断面成像, 视野 220 mm, 层厚 195 mm, 层间距 1.5 mm, 重复 / 回波时间比 =1650/50 ms, GRAPPA R=2, 矩阵128×128, 0 为 265×256 取代。PWI 扫描前以 5 mL/s 的速度静脉注射 Gd-DTPA (马根维显, Bayer HealthCare Pharmaceuticals), 采用单次激发梯度回波弥散横断面成像, 视野 13-195 mm, 层间距 1.5 mm, 重复 / 回波时间比 =1320/50 ms, 矩阵大小和扫描方向与 DWI 相同。轴向涡流自旋回波 T1, T2 加权成像的层数为 19, 重复 / 回波时间比为 680/17 ms(T1 加权) 和 5800/99 ms (T2 加权), 矩阵 128×256(T1 加权) 和 204×256(T2 加权), 视野和扫描方向与 DWI 相同。同时进行了水抑制、梯度回波和血管成像。

图像处理

原始图像的处理由一名研究者 (M.E.K.) 独立操作。将灌注 DICOM 文档输入 Matlab 7.4 软件 (The Mathworks, PGUI 灌注分析软件, CFIN Aarhus University Hospital, 2007), 生成组织反应的峰值时间图。人工选定 DWI 病灶对侧大脑中动脉的动脉输入功能, 用于计算脑血流 (cerebral blood flow, CBF) 和 CBV\(^{[10–12]}\)。PWI 和 DWI 图像采用统计参数制图 (SPM8b; Well-come Trust Centre for Neuroimaging, London, UK) 联合登记。

感兴趣区域分析

将联合登记的图像输入 Analyze 8.1, 用于分析感兴趣区域 (region of interest, ROI)\(^{[3]}\)。DWI 病灶的测量采用了一种自动密度阈值技术。在对侧人工绘制像素 ROI, 测量其 ADC 的平均值。含脑脊液区域的 ADC>120×10⁻⁵ mm²/s, 被排除\(^{[6,14]}\)。病灶与对侧相应区域 ADC 的比例为相对 (Relative, rADC)。

在 CBV 和 CBF 图上将病灶对侧半卵圆中心的正常白质分别标准化为 2 mL/100 g 和 22 mL/100 g/min\(^{[15,16]}\)。CBV>8 mL/100 g 或 CBF>100 mL/100 g/min 的体素视为含血管的区域, 被排除在 ROIs 以外 \(^{[17]}\)。相对 CBF 和 CBV 为 DWI 病灶内与对侧相应区域 CBF 或 CBV 的比值。行 MRI 检查时的灌注状态以 rCBF 衡量。rCBF>0.8(例如 DWI 病灶内的灌流是对侧的 80% 以上) 代表再灌注。

采用 SPM8b 的灰白质图逐层分析所有患者的 T1 加权成像。将 DWI 的 ROIs 和对侧相应区域分为灰质和白质区; 将所有 ROIs 转入 PWI 图计算缺血区域内 CBF 和 CBV 的平均绝对值和相对值 \(^{[18]}\)。

以病灶内 CBV 占对侧相应区域 CBV 的百分位数值所定义的 CBV 阈值来确定缺血区域。在峰值时间图上人工绘制明显异常的 ROIs, 重叠于 DWI 图上。以对侧大脑半球的 CBV 平均值作为正常值, 计算正常值的 5% 、10% 、25% 、50% 、75% 、90% 和 95%。这些百分位数作为 CBV 阈值, 测量峰值时间图上缺血区域的梗死灶体积。

统计学分析

用 SPSS 17.0 进行统计学分析。以线性回归评价 ADC 和 CBV 的相关性, 配对 t 检验比较缺血和对照侧的 DWI 和 PWI 测量值。鉴于患者各种情况迥异, 故根据以下变量对患者进行分组分析: MRI 检查距发病时间 (<9 小时和>9 小时), NIHSS 评分 (<4 分和≥4 分) 和灌注状态 (rCBF>0.8 和 <0.8)。各组间 DWI 和 PWI 的指标用 One-way 方差分析和 post hoc Tukey 检验进行比较。ADC 和 CBV 所界定的缺血灶体积的相关性由 Bland-Altman 点图计算。

结果

基线临床资料

收集了 103 名急性脑梗死患者, 其中 14 名患者因 DWI 无改变而被排除, 35 名患者因缺乏有意义的 PWI 结果而被排除。所以最后纳入了 54 名患者, 其中男性 36 名, 女性 18 名, 平均年龄 71.1±12.1 岁 (41-93 岁)。NIHSS 中位数为 6 (0-27), 其中 NIHSS<4 分的患者 16 名 (30%), 为轻型卒中。发病至 MRI 检查的中位时间 为 13 小时 (0.5-28 小时), 其中 NIHSS<4 分的患者 16 名 (30%), 为轻型卒中。发病至 MRI 检查的中位时间 为 13 小时 (0.5-28 小时), 其中 9 小时以内的患者 21 名 (39%)。22 名患者 (41%) 的 MRI 显示再灌注, 另外 32 名患者为持续低灌注。

DWI 病灶内的 CBV

所有患者 DWI 病灶内的平均 CBV 为 3.3±1.9
而对侧为 4.1±2.1 mL/100 g (P<0.001)。图 1 示不同的 CBV 模式。在 NIHSS ≥4 分的中重度卒中患者，病灶内平均 CBV 较对侧相同区域显著降低 (2.88±1.43 mL/100 g 与 3.2±1.14 mL/100 g, P<0.001, n=38)。而在轻型卒中患者，病灶内与对侧平均 CBV 无显著差异 (3.48±1.61 与 3.43±1.72 mL/100 g, P=0.84, n=16)。轻型卒中患者 DWI 病灶平均体积显著小于中重度卒中患者 (6.7±7.3 mL 与 17.7±2.9 mL, P=0.018)。

灌注效果

持续低灌注患者的 DWI 病灶平均 rCBV (0.79±0.26, n=32) 显著低于再灌注患者 (1.16±0.52, n=22, P=0.029)。CBV 增高 (rCBV>1.0) 见于 15 名再灌注患者 (68%)，而仅见于 4 名持续低灌注患者 (13%)。与之不同的是，所有患者的 rADC 均下降，但低灌注患者下降程度大于再灌注者 (0.69±0.09 与 0.79±0.10, P=0.001)。

MRI 检查距起病时间的影响

以线性回归评价了 ADC 与 CBV 的关系。将所有患者一起分析时，rADC 与 rCBV 无显著相关性 (R=0.20, P=0.30)；分别分析灰质和白质时，ADC 与 CBV 也无相关性 (灰质：R=0.28; P=0.087; 白质：R=0.04, P=0.77)。rADC 与 rCBV 仅在起病时间 <9 小时的患者有显著相关性 (R=0.50, P=0.02, n=21; 图 2)；其中，两者在灰质病灶内仍具有相关性 (R=0.51, P=0.025; 95% 可信区间为 0.022-0.295; n=19, 另 2 名患者病变完全在白质内 )，但在白质内没有 (R=0.42, P=0.056; 95% 可信区间为 -0.002-0.168; 图 3)。在起病时间 >9 小时的患者，rADC 与 rCBV 无显著相关性 (R=0.05, P=0.81)。

rADC 与 rCBV 在轻型 (R=0.01, P=0.85) 或中重度卒中患者 (R=0.04, P=0.49) 无显著相关性，在低灌注 (R=0.09, P=0.63) 或再灌注患者 (R=0.06, P=0.78) 也无显著性差异。

低 CBV 的缺血灶

46 名患者表现峰值时间异常的病灶。以 CBV 阈值所确定的病灶体积与 DWI 病灶体积呈显著相关 (表 1)，两者 95% 可信区间内的平均差值波动在 -11.8 (~1.7 mL; 第 5 百分位数) 至 40.3 (24.6, 56.0 mL; 第 95 百分位数)。较低的 CBV 百分位数倾向于低估 DWI 病灶 (表 2)。在 CBV 第 50 百分位数时两者吻合性较好，仅将 ADC 病灶高估 6.3 (0.1, 12.6) mL (图 4)。在所有的 CBV 百分位数，当梗塞灶较小时，CBV 阈值所确定的病灶体积均倾向于大于 DWI 病灶；而当梗塞灶大时则反之。

讨论

本研究确认了急性脑卒中患者的低灌流与弥散受限相关。但是随着距发病时间的延长，两者的相
关性消失。DWI 所示小病灶，尤其是局限于白质者，可能在 CBV 图上不明显。这些发现有助于将来进行以 CBV 取代 DWI 的研究。

CBV 改变的生理学意义

54 名急性脑梗死患者的 CBV 变化模式是多变的，但大部分患者的 CBV 在 DWI 生物能量降低的区域内降低，并且临床损害越严重降低越显著。部分患者 DWI 病灶内没有相应的 CBV 降低区域，这种 CBV 与 ADC 变化的不匹配与三个因素有关：卒中严重程度、组织类型和距发病时间。

临床表现较轻的患者 DWI 病灶较小，甚至很多患者 CBV 图上未见明确病灶（图 1）。可见 CBV 是一个对于缺血损伤敏感性不高的指标。可能因为在这些病例 CBV 已经被再灌注所校正了，或者因为病灶多局限于白质，而白质的 ADC 与 CBV 的相关性并不显著。

至今另外一例报道进行了 ADC 和 CBV 的比较，仅纳入了 13 名发病 3 小时以内、大的皮质梗死灶的患者[19]，采用了 PWI 和 CTP 技术，发现病灶大小和 CBV 降低存在很强的相关性。而我们的研究样本量较大，患者差异较大，所以 CBV 与 ADC 的关系并非可以简单预测。

DWI 病灶中 rCBF 的增高表明部分患者已经出现再灌注（图 1），但是因为梗死灶已经形成，这种再灌注是非营养性的，与组织的挽救无关[20]。在急性脑血管病综合征的疾病过程中，灌注呈动态变

| 改变的生理学意义               | CBV     | ADC     | 降低区域大小，mL | 腹腔液体 
|--------------------------------|---------|---------|-----------------|---------
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<th>腹腔液体</th>
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化，其中自发再灌注通常出现在发病较长时间以后。但与 PWI 改变不同，ADC 是一种“全或无”现象，一旦达到缺血阈值，无论灌流如何，缺血区域内的 ADC 均下降，鲜有例外[4,21,22]。正是 PWI 与 ADC 的区别导致二者分离，并随着距发病时间的延长而越发显著。

灰质与白质的 CBV 与 ADC

分别评价灰质与白质病变时，发现 rADC 仅在灰质病变中与 rCBV 显著相关，这可能是由于灰质的梗死阈值高于白质[23,24]；另外正常白质的 CBV 已经低于灰质，能够进一步下降的余地较小。

与弥散受限相对应的 CBV 阈值

本研究试图确定基于正常组织百分比的 CBV 阈值，从而预测 DWI 病灶体积。尽管以 50% CBV 为阈值所测量的梗死灶体积能够较好的预测 ADC 受限，不同患者之间仍存在较大差异。已有研究发现 CTP 测量的梗死灶的绝对 CBV 阈值在不同患者也存在变异[9]。因此以单一的 CBV 阈值来检测梗死灶是有欠缺的。

不足

本研究有一些不足之处。与其他 ROI 研究不同，我们的结果因为患者病灶的差异而被复杂化。即便在相同 ROI 内，ADC[25] 和 CBV[18] 也可能不同。所以 DWI 病灶内的各指标平均值不一定能够真实反映不同个体 ADC 和 CBV 的关系。而且 PWI 的获取是基于非弥散示踪动力学，缺血核心的低灌流状态可能导致对 CBV 的错误估计[10]。为了确保捕获对比组织浓度的完整的起伏曲线，我们采用了 98 秒扫描时间，并排除了未能回落至基线的组织浓度曲线。另外本研究的 MRI 数据来自单一时间点，但如果要准确检测卒中后 ADC 和 CBV 随时间的变化模式，需要进行多时点 PWI 扫描。最后，因为临床上难以第一时间进行 MRI 扫描，故常以 CTP 代替 DWI 检测 CBV，所以本研究的结果应同时以 MRI 和 CTP 进行验证。

结论

rCBV 的下降可以预测急性脑梗死灶的弥散异常。CBV 的变化模式随症状严重度和持续时间而变化。本研究的结果支持 CBV 阈值图谱作为 DWI 替代检查方法的继续应用。但是对于距离发病时间较长的患者，CBV 已经恢复正常，此时该方法的应用可能低估不可逆损伤组织的实际体积。

参考文献


表 2 以各个 CBV 百分位数为阈值测定的梗死体积与 DWI 病灶体积的差别

<table>
<thead>
<tr>
<th>CBV 百分位数</th>
<th>ADC-CBV 平均体积, mL</th>
<th>95% 下限</th>
<th>95% 上限</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th</td>
<td>-11.8</td>
<td>-21.9</td>
<td>-1.7</td>
</tr>
<tr>
<td>10th</td>
<td>-11.8</td>
<td>-19.6</td>
<td>-3.9</td>
</tr>
<tr>
<td>25th</td>
<td>-5.3</td>
<td>-11.6</td>
<td>1</td>
</tr>
<tr>
<td>50th</td>
<td>6.3</td>
<td>0.1</td>
<td>12.6</td>
</tr>
<tr>
<td>75th</td>
<td>19.6</td>
<td>9.3</td>
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<tr>
<td>90th</td>
<td>35.9</td>
<td>21.8</td>
<td>50</td>
</tr>
<tr>
<td>95th</td>
<td>40.3</td>
<td>24.6</td>
<td>56</td>
</tr>
</tbody>
</table>

图 4 Bland-Altman 点图显示 ADC 和 CBV 所测梗死体积的区别（正常组织的 50%）。在小梗死灶患者，CBV 所测梗死体积大于弥散成像所测体积 (ADC)。


