Regional Ischemic Vulnerability of the Brain to Hypoperfusion

The Need for Location Specific Computed Tomography Perfusion Thresholds in Acute Stroke Patients

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Background and Purpose—To characterize the spatial pattern of cerebral ischemic vulnerability to hypoperfusion in stroke patients.

Methods—We included 90 patients who underwent admission CT perfusion and MRI within 12 hours of ischemic stroke onset. Infarcted brain lesions ("core") were segmented from admission diffusion-weighted imaging and, along with the CT perfusion parameter maps, coregistered onto MNI-152 brain space, which was parcellated into 125 mirror cortical and subcortical regions per hemisphere. We tested the hypothesis that the percent infarction increment per unit of relative cerebral blood flow (rCBF) reduction differs statistically between regions using regression analysis to assess the interaction between regional rCBF and region variables. Next, for each patient, a "vulnerability index" map was constructed with voxel values equaling the product of that voxel's rCBF and infarction probability (derived from the MNI-152-transformed, binary, segmented, diffusion-weighted imaging lesions). Voxel-based rCBF threshold for core was determined within the upper 20th percentile of vulnerability index map voxel values.

Results—Different regions had different percent infarction increase per unit rCBF reduction (P=0.001). The caudate body, putamen, insular ribbon, paracentral lobule, and precentral, middle, and inferior frontal gyri had the highest ischemic vulnerability to hypoperfusion. A voxel-based rCBF threshold of <0.42 optimally distinguished infarct core in the highly-vulnerable regions, whereas rCBF <0.16 distinguished core in the remainder of the brain.

Conclusions—We demonstrated regional ischemic vulnerability of the brain to hypoperfusion in acute stroke patients. Location-specific, rather than whole-brain, rCBF thresholds may provide a more accurate metric for estimating infarct core using CT perfusion maps. (Stroke. 2011;42:1255-1260.)

Key Words: computed tomography ■ magnetic resonance imaging ■ stroke

There are many factors determining the fate of hypoperfused brain after embolic stroke, including the severity of blood flow reduction, the degree of collateral flow, the time since onset, and the regional sensitivity of the brain to hypoperfusion. Certain brain areas with high baseline metabolic activity, such as the hippocampal CA1 region, are extremely susceptible to reduced oxygen and glucose. It is well-documented that different cellular constituents in gray matter (GM) and white matter are associated with different levels of cerebral blood flow (CBF) and metabolism, providing support for variable vulnerability to hypoperfusion.

Although selective regional ischemic vulnerability has been previously studied, the neuroimaging correlates of this spatial heterogeneity are not established. Determining regional sensitivity can help predict the fate of hypoperfused tissue at highest risk for infarction (ischemic penumbra). Moreover, less vulnerable brain regions may tolerate ischemia for longer times after ictus and, hence, be responsive to delayed therapeutic interventions.

In our study, we evaluated regional ischemic vulnerability of the brain to hypoperfusion in acute stroke patients using admission CT perfusion (CTP) and MRI diffusion-weighted imaging (DWI) scans. CTP is well-suited to quantification of CBF, given the linear relationship between intravenous contrast concentration and CT pixel intensity. First, we performed a regional analysis, examining differences in local percent infarction increment per unit reduction of blood flow, to establish the presence of and determine the locations of

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1255
variable ischemic sensitivity. Next, we constructed a voxel-based “vulnerability map” to visualize this spatial heterogeneity and to determine the voxel-based CTP blood flow thresholds that optimally correlate with infarct core.

Materials and Methods

Patients

Records of all stroke patients who underwent admission CTP and MRI at our center between May 2008 and June 2009 were reviewed. Inclusion criteria were: unilateral first-ever ischemic stroke; admission CTP and MR-DWI scans acquired within 12 hours of symptom onset and within 3 hours of each other; and the absence of any previous brain abnormalities based on admission MRI and clinical history. Our study received Institutional Review Board approval and was compliant with the Health Insurance Portability and Accountability Act.

Image Acquisition

All CT scans were obtained with a multidetector helical scanner (Light Speed; GE Medical Systems). CTP followed noncontrast CT and CTA, comprising a 90-second shuttle-mode acquisition, 1 image per slice every 3 seconds, after intravenous administration of 35 mL nonionic iodinated contrast (7 mL/s). Acquisition parameters were 80 kVp and 200 mAs, covering an 8-cm axial section of 16 adjacent 5-mm slices. Total radiation dose was <450 mSV, which is less than the 500-mSV Food and Drug Administration recommended upper limit. CTP source images were transferred to a GE Advantage workstation for postprocessing using deconvolution-based commercial software (CT Perfusion 3; General Healthcare) without application of voxel-suppression algorithms. A single reference arterial input function was selected semiautomatically as described previously.

MRI was performed on a 1.5-T Signa scanner (GE Medical Systems). Our standard stroke MR protocol includes a DWI sequence with two 180-degree pulses to reduce eddy–current distortions. Repetition time was 5000 ms; echo time was minimal. Axial images were acquired with 5-mm slice thickness and 1 mm interslice gap.

Image Analysis

For MRI, we manually segmented infarct core on admission DWI and developed a binary imaging dataset in which all voxels inside the infarct core were assigned a value of “1” and voxels outside of the core were assigned a value of “0.” These binary DWI lesion maps, along with the CTP parameter maps, were automatically coregistered to the MNI-152 brain space using FLIRT 5.5 (FMRIB Linear Image Registration Tool).

Two series of analyses were performed next: “region-based” and “voxel-based.” The former was used to detect differences in regional percent infarction increment per unit reduction of blood flow to establish the presence of regionally variable ischemic sensitivity in the brain. For the region-based analyses, the CTP and binary DWI lesion images were automatically parcellated into 125 pairs of symmetrical, mirror cortical, and subcortical regions based on the established Talairach atlas using custom-written software programs. Next, the percent infarction and relative CBF (rCBF) were calculated for each transformed region in the symptomatic hemisphere. Linear nonrigid coregistration (transformation) of the binary DWI voxel values (0 or 1) to the MNI-152 brain space resulted in assigned fractional voxel values between 0 and 1, reflecting the probability of infarction for that voxel. Because the voxels of differently shaped brains map (spatially transform) to slightly different voxel coordinates on the MNI-152, a single dichotomized value for the presence or absence of infarction becomes inappropriate. Regional percent infarction was defined as the mean of the infarction probability voxel values for each Talairach-defined region. The rCBF value for each region was determined as the ratio of the mean absolute CBF of that region in the symptomatic hemisphere, divided by the mean absolute CBF of the corresponding contralateral mirror region.

Voxel-based vulnerability maps were constructed for each patient in the MNI-152 space. The voxel-based rCBF values were calculated in an analogous manner to the regional values. For each voxel, the vulnerability index (VI) was defined as the product of the voxel-based rCBF value and the probability of infarction in that voxel. Thus, voxels with a high probability of infarction despite high CBF had the highest VI values, whereas voxels with low probability of infarction despite low ischemic flow had the lowest VI values. The vulnerability map voxel values for each patient were overlaid onto the MNI-152 brain space, and mean VI values per voxel were calculated across all patients.

To demonstrate the spatial distribution of cerebral infarction in our patients, we developed an MNI-152–based brain map in which each voxel value equaled the mean infarction probability in that particular voxel, stratified by quintiles.

Statistical Analysis

In a pooled regression analysis, we first evaluated whether there was a linear relationship between the regional rCBF and percent infarction across all regions and patients. Then, multivariate regression analysis was applied to the region-based dataset to test the hypothesis that percent infarction increment per unit rCBF reduction differs statistically between the 125 paired parcellated brain regions. A regression model was constructed correlating percent infarct volume within each brain region with the following input variables: (1) regional rCBF; (2) an arbitrary categorical variable representing each region; and (3) an interaction term between the first 2 variables. A significant probability value in the interaction term of the model (rCBF × region) would support the hypothesis that percent infarct volume increment per unit rCBF reduction differs statistically between the brain regions.

We determined the brain regions with highest ischemic vulnerability using simple linear regression. For each region, the linear regression equation correlating regional percent infarction with regional rCBF was calculated. The slope of the regression line, B, reflects the increase in regional percent infarction per unit reduction in blood flow (higher slopes [|B|] suggest greater ischemic vulnerability).

For the voxel-based analyses, we determined the optimal pooled voxel-based rCBF thresholds that could distinguish infarct core from noninfarcted brain on the segmented admission DWI scans using receiver-operating characteristics curve analysis. First, we determined the optimal threshold at the operating point of the receiver-operating characteristics curve for the pooled voxels located within the upper 20th percentile of the VI voxel values on the mean vulnerability map. Next, we determined the threshold for the pooled voxels in the remainder of the brain.

All values were expressed as either percentages or means ± SD. Statistical analyses were performed using STATA 10.

Results

We included 90 patients with acute first-ever unilateral stroke. Of these, 51 (57%) had left hemispheric stroke and 54 (60%) were male. Based on the admission CTA imaging reports, 72 (80%) patients had anterior circulation arterial occlusion (7 anterior cerebral artery, remainder middle cerebral artery), 6 (7%) had posterior circulation occlusion, and 12 (13%) had no visible occlusion. The majority of patients in our study had infarction in the middle cerebral artery territory (Figure 1). Admission CTP scans were performed 0.5 to 8.5 hours after stroke onset (mean, 3.7 ± 2.0), and MRI scans followed CTP within 0.2 to 2.7 hours (mean, 0.4 ± 0.3). There was a significant linear relationship between regional percent infarction and rCBF across all regions and patients ($R^2 = 0.35; P < 0.001$).

The multivariate regression model showed a strongly significant interaction between rCBF and the region vari-
ables, confirming that regional percent infarction increment per unit \( rCBF \) reduction differs statistically between parcelated regions \( (P<0.001; \text{Table 1}) \) and, hence, that ischemic vulnerability varies between locations.

This regional variability was also shown by simple linear regression for each of the 125 paired parcellated brain regions. Overall, regional percent infarction increased with decreasing \( rCBF \). Table 2 lists those regions with highest slope of the regression line corresponding to greatest ischemic vulnerability \( (|B|=\beta \), coefficient, increase in regional percent infarction per unit reduction in blood flow). The corpus callosum had the lowest \(|B|\) values \( (|B|=0.10; R^2=0.23 \text{ left}; |B|=0.03; R^2=0.30 \text{ right}) \), whereas the insula, precentral gyrus, and basal ganglia had the highest \(|B|\) values.

Voxel-based analysis provided visual corroboration of the region-based results (Figure 2). On the mean vulnerability map, the basal ganglia, insula, precentral gyrus, paracentral lobule, middle frontal, and inferior frontal gyri appear highly vulnerable bilaterally. Based on operating point receiver-

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**Table 1. Multivariate Regression Analysis to Test the Hypothesis That Percent Infarction Increment per Unit Relative Cerebral Blood Flow Reduction Differs Statistically Between the 125 Paired Parcellated Brain Regions**

<table>
<thead>
<tr>
<th>( rCBF )</th>
<th>( \beta )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>SE</td>
<td>( \beta )</td>
</tr>
<tr>
<td>rCBF</td>
<td>0.535</td>
<td>0.487</td>
</tr>
<tr>
<td>Region</td>
<td>0.063</td>
<td>0.003</td>
</tr>
<tr>
<td>rCBF ( \times ) region</td>
<td>-0.057</td>
<td>0.004</td>
</tr>
<tr>
<td>Constant</td>
<td>2.96</td>
<td>0.426</td>
</tr>
</tbody>
</table>

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**Table 2. Brain Regions With Highest Ischemic Vulnerability to Hypoperfusion**

<table>
<thead>
<tr>
<th>Regions</th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate body</td>
<td>0.94</td>
<td>0.84</td>
</tr>
<tr>
<td>Putamen nucleus</td>
<td>0.79</td>
<td>0.85</td>
</tr>
<tr>
<td>Insular ribbon</td>
<td>1.30</td>
<td>1.15</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>0.82</td>
<td>0.95</td>
</tr>
<tr>
<td>Frontal lobe subcortical white matter</td>
<td>0.78</td>
<td>0.91</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>1.30</td>
<td>1.15</td>
</tr>
<tr>
<td>Frontal lobe paracentral lobule</td>
<td>0.74</td>
<td>1.04</td>
</tr>
</tbody>
</table>

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**Figure 1.** Topographical distribution of infarction in our patients. Voxel values reflect the mean probability of infarction for that voxel across all patients. Color scale is based on stratification by quintile groupings.

**Figure 2.** Mean voxel-based regional ischemic vulnerability of the brain on a color scale for 90 patients. After nonrigid transformation of the segmented diffusion-weighted imaging infarct lesion maps to the MNI-152 brain space, each voxel was assigned a value from 0 to 1 as the infarction probability. For each patient, vulnerability index values in each voxel were calculated as the product of the infarction probability and the relative cerebral blood flow.
operating characteristics curve analysis of those voxels with VI values within the upper 20th percentile (i.e., highly vulnerable locations; Figure 3), a voxel-based rCBF threshold of 0.42 optimally distinguished infarct core. In the remainder of the brain, an rCBF voxel threshold of 0.16 distinguished infarct core with similar sensitivity and specificity.

Discussion
We have shown that ischemic vulnerability varies across brain regions, and that the caudate, putamen, insula, precentral gyrus, inferior frontal, and middle frontal gyri are among the locations most highly sensitive to reductions in CBF. We have quantified that, for our particular CTP acquisition protocol and postprocessing software, \( \approx 60\% \) reduction in rCBF in these highly vulnerable locations distinguishes infarct core, whereas \( \approx 85\% \) reduction in rCBF distinguishes infarct core in the remainder of the brain.

The literature supports our findings. Previous studies in rats have shown higher frequency of DWI changes in the hippocampus, cortex, and caudate/putamen, and greater degree of selective neuronal loss in the caudate/putamen after unilateral hypoxia-ischemia. Cheng et al also have reported higher probabilities of infarct growth in the striatocapsular region of stroke patients with middle cerebral artery stem occlusion. Interestingly, the spatial pattern of sensitivity to hypoperfusion in our patients (Figures 2 and 3) resembles the topographical distribution of early DWI hyperintensities reported in patients with hypoxic-is-

Figure 3. Regional ischemic vulnerability of the brain dichotomized into highly vulnerable (shaded voxels) vs less vulnerable (remainder of the brain) locations. A voxel-based relative cerebral blood flow (rCBF) threshold of \( <0.42 \) optimally differentiated infarct core in the highly vulnerable regions (voxels within the upper 20th percentile of values on the vulnerability map; area under receive-operating characteristics curve [AUC], 0.72; 54% sensitivity, 80% specificity; \( P<0.001 \); bottom left), whereas an rCBF threshold of \( <0.16 \) distinguished core in the remainder of the brain, with equal sensitivity and specificity (AUC, 0.73; 54% sensitivity; 79% specificity; \( P<0.001 \); bottom right).
chemic encephalopathy. This suggests the possibility that similar pathophysiological mechanisms of regionally selective neuronal loss may underlie cerebral injury in patients with embolic-occlusive and hypoxic-ischemic stroke.

There also are well-documented differences in the neurochemical response to ischemia of white matter versus GM, likely attributable to greater metabolic demands of GM. Within GM, certain cortical regions in our study appeared more vulnerable than others, including the insular, precentral, and inferior frontal gyri. The specific cortical areas with the highest ischemic sensitivity to hypoperfusion displayed on our mean vulnerability map (Figure 2) and regional regression results (Table 2) could, in part, be attributed to the high volume of convoluted GM at these locations. Our results also may reflect selective neurophysiologic vulnerability of these regions. In support of this latter hypothesis, Woo et al found selective cerebral GM loss in the frontal and insular cortices of patients with long-term heart failure, presumably attributable to ischemia accompanying perfusion deficits.

The vulnerability map of the brain reveals subtle topographical asymmetry (eg, of the frontal paracentral lobules; Figure 2 and 3) that may be artifactual; however, there may be other explanations for these findings. The inhomogeneous distribution of infarction in our patients (Figure 1) and/or the presence of outliers could contribute to this asymmetry, or it might reflect true asymmetrical vulnerability of these regions.

In agreement with previous studies, our rCBF threshold for infarct core was much higher (<0.42) in vulnerable cerebral areas versus the rest of the brain (<0.16). Arakawa et al reported CBF thresholds of 34.6 mL/100 g/min for GM and 20.8 mL/100 g/min for white matter in an MR perfusion study. Bristow et al found CBF thresholds of 20.0 mL/100 g/min and 12.3 mL/100 g/min for infarction in GM and white matter, respectively. Optimal CTP parameter thresholds for infarct core can vary significantly between vendors and even between different software from the same vendor. The optimal rCBF threshold (0.16) that we found in this study for less vulnerable brain voxels is in agreement with thresholds previously reported for an independent cohort who underwent a 65-second acquisition with postprocessing by the same software using the same default parameters (CT Perfusion 3).

Given the variability in absolute quantification with different software, we chose to report relative, rather than absolute, values. Although rCBV as a surrogate for infarct core is well-established, in our study we sought to study ischemic vulnerability based on the degree of hypoperfusion. The intrinsic physiological variability of CBV changes with ischemia, which include such phenomenon as luxury perfusion and elevated CBV attributable to autoregulatory mechanisms, make CBV a less desirable parameter given the aims of our study. Previous work also has suggested that CBV measurements are likely more sensitive to subtle differences in acquisition and postprocessing protocols than are CBF measurements.

Our findings may have clinical implications. Although we did not include time after ictus in our models, it is reasonable to hypothesize that less vulnerable areas may have a longer therapeutic time window for reperfusion treatment. This also may suggest that for those patients with ischemia at the most highly vulnerable brain locations, even early robust recanalization might be more effective if accompanied by neuroprotective therapies.

There are a number of limitations to our study. Our results are limited by the spatial distribution of stroke lesions in our cohort (Figure 1). We could not evaluate voxels that had few or no infarctions, most notably in the posterior circulation. The variable time between stroke onset, admission CTP, and admission DWI for different patients also may have distorted our results. Moreover, because CTP quantification is not yet standardized between different acquisition and postprocessing protocols from different vendors, the rCBF thresholds we report could vary slightly between different imaging platforms. Although the choice of a 20% cut-off in Figure 3 was arbitrary, this allowed us to visually threshold the “most” highly vulnerable regions for demonstration purposes.

Finally, the difference between our reported CBF thresholds and those of the literature is likely attributable to both differences in CTP acquisition length (45 seconds versus >65 seconds in current generation protocols), and that we did not apply vessel exclusion postprocessing algorithms to be consistent with our current clinical defaults and to maximize contrast-to-noise ratio. This suggests that the specific thresholds that we report may have limited generalizability to other acquisition and postprocessing platforms.

Conclusions

In conclusion, we have shown regional differences in ischemic susceptibility of the brain to hypoperfusion. Of the territories with infarction in our cohort, we found that the caudate and putamen were highly vulnerable, as were specific cortical areas, including the insula, precentral gyrus, and middle and inferior frontal gyri. Our findings support the hypothesis that location-specific thresholds may be more accurate than whole-brain thresholds for estimating the likelihood of infarction with CTP and, hence, have the potential to be of value in clinical management.

Sources of Funding

This work was supported by the Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) grant funded by the National Institute of Health (NIH; P50 NS051343), the Agency for Healthcare Research and Quality grant AHRQ R01 HS11392, and the Massachusetts General Hospital Clinical Research Center (1 UL1 RR025758–01), Harvard Clinical and Translational Science Center, from the National Center for Research Resources.

Disclosures

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References


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Background and Purpose: To describe the spatial distribution of local ischemic vulnerability of the brain to hypoperfusion in acute stroke patients.

Methods: We selected 90 patients with stroke within 12 hours who underwent both CTP and DWI. On the DWI, the infarct core was delineated, and a parameter map of CTP was overlaid on MNI-152 space. The brain was divided into 125 cortical and subcortical regions. Regression analysis was performed to assess the relationship between the relative CBV and the percentage of lesion. We verified the assumption that different brain regions differ in their vulnerability to change in rCBV. For each patient, the “vulnerability map” was constructed based on voxel rCBV and lesion probability. The threshold of voxel rCBV was set at the 20th percentile for the vulnerable core region, and rCBF below 0.16 was set as the threshold for unaffected regions.

Results: The percentage of lesion increased with decreasing rCBV in different brain regions (P = 0.001). The highest vulnerability was found in the caudate, putamen, insula, paracentral lobule, precentral gyrus, and superior frontal gyri. The voxel rCBV threshold was set at 0.42 for the vulnerable core region, and rCBF below 0.16 was set as the threshold for unaffected regions.

Conclusion: We validated the local ischemic vulnerability of the brain to hypoperfusion in acute stroke patients. CTP rCBV thresholds provided a more precise measurement of the vulnerable core region, but their use has regional specificity and is not applicable to the whole brain.

Keywords: Computed tomographic perfusion, magnetic resonance imaging, stroke (Stroke. 2011;42:1255-1260. 吉林大学第一医院神经内科 孙莉 译 杨弋 吴江 校)
材料和方法

患者

研究中我们回顾了医疗中心2008年5月到2009年6月就诊的行CTP和MRI检查的脑卒中患者。

入选标准：单侧首发的缺血性脑卒中；症状出现12小时内行头部CTP及MR-DWI检查；既往史及头部MRI检查否认存在任何脑部疾病史。我们的研究得到了国家学术审查委员会的批准，并符合健康保险与责任法案的规定。

影像采集

所有的CT扫描均由多层螺旋扫描仪获取。行头部CT平扫及CT血管造影（CTA）后，行CTP检查，静脉注入35mL非离子型等渗碘对比剂后，每3秒钟完成一帧图像的扫描，由90秒模式获得的图像构成CTP检查。采集参数分别是管电压80kVp、管电流200mAs, 沿8cm的中轴分为16个相邻的5mm厚的层面。总辐射剂量<450mSv, 低于食品和药物管理局规定的上限500mSv[2]。然后将CTP影像移至GE工作站用重叠法商务软件（CT Perfusion 3; General Healthcare）进行后处理，而不是运用除外血管的方法计算[3]。

MRI运用1.5 T的Signa扫描仪（GE Medical Systems）完成。我们标准的MR卒中协议包括带有2个180度脉冲的DWI序列以减少涡流的扭曲效应。重复时间为5000ms; 反射时间最小。轴向图像采用5mm的层厚和1mm的间隔厚度扫描。

图像分析

对于MRI，我们手动在DWI相上对梗塞灶进行分割并形成一组双相的数据集。这个数据集中梗塞灶里的所有体素均赋值为“1”，梗塞灶外的体素赋值为“0”。使用FLIRT 5.5软件（FMRIB线性图登记工具）自动地把这些二元的DWI损伤图，连同CTP参数图标注在MNI-152脑空间图上。

其次进行如下两个序列的分析：基于区域和基于体素的分析。前者用于监测随每单位血流量的减少，区域梗塞百分比增加的不同，以确定脑内不同区域缺血敏感性的差别。对于以区域为基础的分析，在用传统书写软件（custom-written）程序构建的Talairach图集的基础上，自动地把CTP和二元的DWI相损伤图分成125对对称的、皮质和皮质下区域。此外，计算有症状半球每个转化区域的梗塞百分比和相对脑血流量（rCBF）。将二元的DWI体素值（0或1）线性转化到MNI-152脑空间图中，以求于把部分体素值分配于0-1之间，此值反映了相应体素发生梗塞的概率[4]。因为不同的脑图整合到MNI-152上，体素会有差异，因此单纯的用是与否判断梗塞灶是否存在是不合适的。对于每个Talairach定义的部位，区域梗塞百分比被认为是梗塞概率体素值的均数。每个脑内部位rCBF值被确定为有症状侧半球该部位与对侧相应部位的平均绝对CBF的比率。

本研究为每个患者在MNI-152空间图上构建了以体素为基础的易损图。用类似于计算区域值的方法计算以体素为基础的rCBF值。对于每个体素来说，易损指标被定义为以体素为基础的rCBF值和该体素梗塞概率的乘积。因此，梗塞概率高的体素尽管rCBF高却有最高的易损指数（VI）值，而梗塞概率低的体素尽管低血液流量却有最低的VI值。每个患者易损图的体素值被标在MNI-152脑空间图上，且计算出了所有患者每个体素的平均VI值。

为展示研究中患者的脑梗塞空间分布，我们开发了一个以MNI-152为基础的脑图，图中每个体素值代表梗塞的平均概率。

统计分析

在综合性的回归性分析中，我们首先在所有区域和患者中进行分析，以评价局部rCBF和梗塞百分比之间是否存在线性关系。然后为了验证随每单位rCBF的减少，梗塞百分比的增加在被分出的125对脑组织中是不同的，研究者对以区域为基础的数据集进行了多变量回归分析。研究人员构建了一个回归模型，这一模型在每个脑内区域将梗塞容积百分比与如下输入变量相联系：（1）区域的rCBF；（2）代表每一大脑区域的任意类别变量；（3）前两个变量的交感项。该模型中交感项（rCBF×区域）的一个显著概率值会支持脑内各区域中，随每单位rCBF的减少梗塞容积百分比增加不同的这一假设。

我们用简单线性回归确定脑内缺血易损性最高的区域。每一区域，我们都用线性回归方程评估缺血百分比与局部脑血流量之间的关联。回归线的斜率（|B|）反映了血流量每减少一单位区域，梗塞百分比的增加（|B|越高说明缺血易损性越高）。

对于体素为基础的分析，我们制定了最佳的基于体素的rCBF阈值，使用接收-操作特性曲线分析时，这一阈值在DWI相分段的扫描中能区分出梗塞区和非梗塞区。首先，我们在接收-操作特性曲线上的作用点确定最佳阈值，在平均易损图上将易损
表 1 多元回归分析以验证在 125 对脑内区域随 rCBF 的减少，梗塞百分比增加的情况

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF</td>
<td>0.535</td>
<td>0.487</td>
<td>0.019</td>
<td>0.273</td>
</tr>
<tr>
<td>部位</td>
<td>0.063</td>
<td>0.003</td>
<td>0.279</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rCBF × 部位</td>
<td>-0.057</td>
<td>0.004</td>
<td>-0.344</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>恒量</td>
<td>2.96</td>
<td>0.426</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

用上表中的 3 个变量构建与每个脑内区域相关脑的梗塞容积百分比回归模型。交感项 (rCBF × 部位) 支持不同部位的梗塞易损性不同的假设。统计, 在分出的 125 对不同脑区域中，随每单位 rCBF 的减少，梗塞容积百分比增加不同。

### 结果

我们的研究纳入了 90 名首次发作单侧急性脑卒中的患者。这些患者中，有 51 名 (57%) 是左侧半球脑卒中，54(60%) 名为男性。头部 CTA 报告显示，前循环动脉闭塞者 72 名 (80%)，7 个大脑前动脉，后循环动脉闭塞者 6 名 (7%)，12 名 (13%) 未见明显的血管闭塞。研究中大部分患者存在大脑中动脉供血区的梗塞 (见图 1)。入院头部 CTP 检查在脑卒中后 0.5-8.5 小时内完成 (平均时间 3.7±2.0)，头部 MRI 在行 CTP 检查后 0.2-2.7 小时 (平均时间，0.4±0.3) 内完成。所有结果均显示区域梗塞百分比和其 rCBF 之间存在线性关系 (R²=0.35; P<0.001)。

多元回归模型显示 rCBF 和局部变量之间存在显著性相关性，统计证实不同区域随每单位 rCBF

余均未为大脑中动脉；后循环动脉闭塞者 6 名 (7%)；12 名 (13%) 未见明显的血管闭塞。研究中大部分患者存在大脑中动脉供血区的梗塞 (见图 1)。入院头部 CTP 检查在脑卒中后 0.5-8.5 小时内完成 (平均时间 3.7±2.0)，头部 MRI 在行 CTP 检查后 0.2-2.7 小时 (平均时间，0.4±0.3) 内完成。所有结果均显示区域梗塞百分比和其 rCBF 之间存在线性关系 (R²=0.35; P<0.001)。

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的减少，区域梗塞百分比增加不同 (P<0.001，表 1)，因此不同部位缺血易损变量亦不同。

这种区域变异性在被分出 125 对区域的每部分脑组织中，可通过简单的线性分析显示出来。总的来说，区域梗塞百分比随着 rCBF 的减少而增加。表 2 列举了回归线斜率最高的区域，与缺血易损性最敏感的部位相一致 (斜率 = |B| 系数，随每单位血流量的减少，区域梗塞百分比增加)。胼胝体的斜率值最低 (左 侧 |B|=0.10；R²=0.23；右侧 |B|=0.03；R²=0.30)，而脑岛、中央前回和基底神经节斜率值最高。

基于体素的分析结果为以区域为基础的结果 (图 2) 提供了直观的证据。在平均易损率脑地图上，基底神经节区、脑岛、中央前回、旁中央小叶、额中回、额下回均呈现出较高的易损性。基于对这些 VI 值在第 20 百分位以上的 (例如：高易损区) 体素的工作点受试者操作特征性曲线的分析，基于体素的 rCBF 阈值为 0.42 最适于识别缺血灶。其他部位脑组织，基于体素的 rCBF 阈值为 0.16 对于鉴别梗塞灶有较高的敏感性和特异性。
讨论

我们的研究显示了不同脑组织的缺血易损性不同，且尾状核、壳核、岛叶、中央前回、额下回及额中回是对缺血最敏感的区域。借助特有的 CTP 获取协议和后处理软件，我们对数据进行了量化统计，在高度易损部位，rCBF 减少约 60% 即能鉴别出梗塞灶，而脑内其他部位 rCBF 减少约 85% 才能被鉴别。


我们的实验研究有一定的临床意义。尽管在我们的研究模式中未计发作后时间，但是相对不易受损区域再灌注治疗的时间窗更长的假设是合理的。这还提示我们：对于发生在高度易损区的脑缺血患者来说，如果同时给予神经保护治疗，对早期的血管再通可能更有效。

这项研究有一定的局限性，研究结果也受到入组群体脑梗塞部位空间分布的限制(图 1)。另外，我们不能对那些仅有少量或无梗塞灶的体素值进行评估。不同的患者卒中起病、接受 CTP 检查及 DWI 成像的时间上的多变性也会影响我们的实验结果。此外，CTP 数据的获取方式不同，后处理模式的供应商也可能不同，这些均未经标准化处理，故我们报道的 rCBF 阈值由于不同的影像资料来源也会有轻微的变化[13]。尽管对图 3 所示的 20% 界限的选择是随机的，但这使我们直观的看到了最高易损区的阈值。

最后，我们报道的 CBF 阈值与文献报道数值之间的不同可归因于二者 CTP 获得时间的长短不同造成的 (45 秒和当前方案中的 >65 秒)，且我们并没有使用额外血管的后处理计算法，故我们报道的 rCBF 阈值由于不同的影像资料来源也会有轻微的变化[13]。尽管图 3 所示的 20% 限额的选择是随机的，但这使我们在直观的看到了最高易损区的阈值。

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在认同既往研究的基础上，我们评估的易损脑组织梗塞灶的 rCBF 阈值 (<0.42) 较脑内其他部位 (<0.16) 高出许多。Arakawa 等人[11]在一项 MR 灌注研究中报道灰质 CBF 阈值为 34.6 mL/100 g/min，白质为 20.8 mL/100 g/min。Bristow 等人 [12] 发现灰质、白质区域梗塞灶的 CBF 阈值分别是 20.0 mL/100 g/min、12.3 mL/100 g/min。仪器供应商不同得到的评估梗塞灶的 rCBF 参数阈值可能有所不同，甚至来自同一供应商的不同软件得到的结果也会不同。本研究发现，不易受损的脑组织最佳 rCBF 阈值 (0.16) 与既往一项研究报道的阈值相符，这项报道是对一个独立的群体，获取 >65 秒的影像数据，通过相同的软件用相同的默认参数 (CT 灌注 3) 进行后处理 [13]。

介于不同软件可得出不同的量化值，我们选择报道相对的而非绝对的测试值[14]。尽管已经确定 rCBV 可以作为梗塞核心区的替代项，但是在我们的研究中我们倾向于在低灌注情况下研究脑组织的缺血易损性。由于人体的自身调节机制，伴随缺血时 CBV 变化的内在生理学改变可能被掩盖。考虑到我们的研究目的，故把 CBV 作为一个次要参数[15]。先前的工作也提示在获取和后处理协议中，CBV 的测定对于轻微的差异比 CBF 更敏感。

我们的实验研究有一定的临床意义。尽管在我们的研究模式中并未计入发作后时间，但是相对不易受损区域再灌注治疗的时间窗更长的假设是合理的。这还提示我们：对于发生在高度易损区的脑缺血患者来说，如果同时给予神经保护治疗，对早期的血管再通可能更有效。

结论

综上，我们表明了低灌注时脑组织缺血敏感性的区域差异。在我们研究群体的梗塞灶所在区域中，我们发现尾状核和壳核极易受损，一些特殊皮质区，包括脑岛、中央前回、额中回及额下回亦易受损。
此项研究结果支持以下假设：在用 CTP 评估梗塞发生的可能性时，区域特异性阈值可能比全脑阈值更为准确。因此，区域特异性阈值在临床中具有很好的应用前景。

参考文献