Cerebral Blood Flow Is the Optimal CT Perfusion Parameter for Assessing Infarct Core

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Background and Purpose—CT perfusion (CTP) is widely and rapidly accessible for imaging acute ischemic stroke but has limited validation. Cerebral blood volume (CBV) has been proposed as the best predictor of infarct core. We tested CBV against other common CTP parameters using contemporaneous diffusion MRI.

Methods—Patients with acute ischemic stroke <6 hours after onset had CTP and diffusion MRI <1 hour apart, before any reperfusion therapies. CTP maps of time to peak (TTP), absolute and relative CBF, cerebral blood flow (CBF), mean transit time (MTT), and time to peak of the deconvolved tissue residue function (Tmax) were generated. The diffusion lesion was manually outlined to its maximal visual extent. Receiver operating characteristic (ROC) analysis area under the curve (AUC) was used to quantify the correspondence of each perfusion parameter to the coregistered diffusion-weighted imaging lesion. Optimal thresholds were determined (Youden index).

Results—In analysis of 98 CTP slabs (54 patients, median onset to CT 190 minutes, median CT to MR 30 minutes), relative CBF performed best (AUC, 0.79; 95% CI, 0.77–0.81), significantly better than absolute CBV (AUC, 0.74; 95% CI, 0.73–0.76). The optimal threshold was <31% of mean contralateral CBF. Specificity was reduced by low CBF/CBV in noninfarcted white matter in cases with reduced contrast bolus intensity and leukoaraiosis.

Conclusions—In contrast to previous reports, CBF corresponded with the acute diffusion-weighted imaging lesion better than CBV, although no single threshold avoids detection of false-positive regions in unaffected white matter. This relates to low signal-to-noise ratio in CTP maps and emphasizes the need for optimized acquisition and postprocessing. (Stroke. 2011;42:3435-3440.)

Key Words: CT perfusion ■ diffusion-weighted imaging ■ stroke ■ thrombolytic therapy

Advanced imaging of acute ischemic stroke has the potential to expand eligibility for thrombolysis beyond rigid time window-based selection. MRI perfusion–diffusion mismatch has been proposed as a method to identify patients likely to have salvageable brain tissue and therefore potentially benefit from reperfusion.1,2 The clinical application of MRI has, however, been impeded by limited emergent access to scanners. CT perfusion is a contrast bolus-tracking technique that can be performed on virtually any multidetector CT scanner currently in service in emergency departments throughout the world.3,4 To date, however, there have been limited studies of CT perfusion parameters and thresholds that optimally define irreversible infarction, a critical parameter in predicting the risks and potential benefits of reperfusion therapies.5 This is in contrast to MRI in which diffusion imaging has recently been confirmed as a reliable indicator of irreversible infarction.6,7,8a Previous research based on ROC analysis of concurrent diffusion MRI and CT perfusion in 25 patients9 proposed that absolute cerebral blood volume (CBV) <2.0 g/100 mL was the optimal method to determine infarct core. One study of 14 patients treated with intra-arterial thrombolysis suggested that relative cerebral blood flow (CBF) might be better than CBV.9 Other analyses have demonstrated correlation between infarct volume on MRI with empirical thresholds of cerebral blood volume10,11 but did not systematically compare parameters. CT perfusion has lower signal to noise compared with MRI, necessitating significant postprocessing (smoothing) of the data. This currently varies between CT perfusion processing software packages.12 We therefore aimed to systematically examine the effect of smoothing and determine the optimal parameter and threshold for irreversible infarct core in a larger series of patients with contemporaneous diffusion MRI and CT perfusion.

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Methods

Patients

Consecutive patients with acute ischemic stroke within 6 hours of stroke onset at a single center had diffusion MRI (1.5-T Siemens Magnetom Vision) obtained <1 hour after CT perfusion (CTP). Both imaging modalities were acquired before thrombolysis. The study was conducted from 2003 to 2007 and was approved by the institutional ethics committee. All patients gave written informed consent.

CT Acquisition

CTP was acquired (16-slice Phillips Mx8000 scanner) as 2 separate 24-mm slabs positioned to maximize supratentorial coverage. Undiluted contrast (40 mL) was injected at 5 mL/s and 35 images acquired every 1.3 seconds (total acquisition time 45 seconds). CT angiography was performed after CTP. Baseline major vessel occlusion was rated for site: internal carotid artery; middle cerebral artery—proximal (M1) or distal (M2); anterior or posterior cerebral artery; and severity using Thrombolysis In Myocardial Ischemia grade by consensus of 2 stroke neurologists (B.C.V.C. >5 years’ experience, M.W.P. >10 years’ experience).

CTP Analysis

Because commercial image processing software packages use a variety of postprocessing techniques, which are often incompletely specified and usually not customizable, we developed our own image processing pipeline using open-source MINC tools (Montreal Neurological Institute) and in-house developed Matlab scripts (R2009b; Mathworks, Natick, MA). Automated motion correction (in-plane) was performed and the raw CTP data were downsampled (bicubic without antialiasing) from 512×512 to 256×256. Gaussian smoothing was applied to the raw data using a range of kernel widths from 0 to 10 pixels (0–9.1 mm radius). All nonbrain tissue voxels were excluded from the kernel weighting to avoid edge smearing. An arterial input function was selected from the anterior cerebral artery and venous outflow function (VOF) from the superior sagittal sinus by a user-supervised (B.C.V.C.) arterial input function detection algorithm. Singular value decomposition deconvolution was performed with standard (sSVD, delay-sensitive) and oscillatory index—regularized block circular (oSVD, delay-insensitive) algorithms to create maps of CBF, mean transit time (MTT), and time to peak (Tmax). CBV and TTP were calculated from the concentration–time curve. CBV and CBF were calculated both as absolute quantities and relative (by ratio) to the mean of the contralateral hemisphere. TTP was expressed relative (by offset) to the mean of the contralateral hemisphere. For quality control, the visual appearance and peak was expressed relative (by offset) to the mean of the contralateral hemisphere. TTP curve. CBV and CBF were calculated both as absolute quantities and regularized block circular (oSVD, delay-insensitive) algorithms to

Coregistration and Regions of Interests

The diffusion MRI was coregistered to each CTP slab using the noncontrast CT as an intermediary (MINC tools) and visually verified for accuracy using interactive image blending (B.C.V.C.). The maximal visual extent of the coregistered diffusion lesion and relative TTP lesion were manually outlined (B.C.V.C.). These manual regions of interest were drawn without reference to other imaging over a 1-week period and independently verified by a second stroke neurologist (M.W.P.) with disagreements resolved by consensus. Patients were included in this analysis if at least 1 CT perfusion slab contained abnormal perfusion and a component of the coregistered diffusion lesion. Patients were excluded if the contrast bolus arrived before the start of the acquisition or did not give rise to a detectable arterial input function.

ROC Analysis

ROC analysis was performed to assess the discriminative power of each perfusion parameter with respect to the coregistered concurrent diffusion-weighted imaging lesion as reference standard following the method of Christensen et al and detailed in an online supplement (Supplemental Methods; http://stroke.ahajournals.org). CIs for the global AUC statistics were derived by bootstrapping 10 000 random samples with replacement. The performance difference between CBF and CBV was also assessed by measuring sensitivity, specificity, positive/negative predictive values, and the median volume of contralateral false-positive tissue below threshold (Wilcoxon).

Results

Contemporaneously acquired CTP and diffusion MRI were available from 64 consecutive sub-6-hour patients with ischemic stroke (126 CTP slabs). Of these, 98 slabs from 54 patients were analyzed after exclusion of 18 slabs that did not cover a region of abnormal perfusion, 8 that did not cover a region of diffusion abnormality, and 2 with inadequate contrast bolus. The mean age of the patients was 71.8 years (SD 11.3) and 48% were male. Baseline major vessel occlusion (Thrombolysis In Myocardial Ischemia [TIMI] grade 0–1) was present in 81% (17% internal carotid artery, 57% proximal middle cerebral artery, 9% distal middle cerebral artery). The median time to CT was 190 minutes (interquartile range, 183–232 minutes) and median time between CT and MR was 27 minutes (interquartile range, 25–35 minutes).

ROC Analysis

The visual effect of smoothing the raw data on perfusion maps (sSVD) is illustrated in Figure 1 and was associated with improved global AUC values for all map types (Figure 2). Relative CBF had the highest AUC followed by absolute CBF, relative and absolute CBV, and the time-based parameters TTP, Tmax, and MTT. The global optimal thresholds from Youden index (Table 1) also shift with increasing smoothing. The AUC values for maps produced using oSVD were slightly lower for an equivalent level of smoothing due to increased noise. As expected, the optimal thresholds for CBF (but not other parameters) also differed using delay insensitive oSVD (Supplemental Table I).

A smoothing kernel of 6 pixel width (5.5-mm radius) was felt to be optimal based on the plateau in AUC and optimal threshold values at this level as well as the excessively blurred visual appearance created by wider kernels. Using these maps, CIs for the global AUCs were generated using bootstrapping. The 95% CIs for relative CBF (AUC, 0.79; 95% CI, 0.77–0.81) did not overlap those of any other parameter, including the previously proposed absolute CBV (AUC, 0.74; 95% CI, 0.73–0.76). The difference in AUC between relative CBF and absolute CBV was significant (mean, 0.05; 95% CI, 0.029–0.059; P<0.001, sign test). The optimal threshold for infarction using relative CBF (sSVD) was 31% (95% CI, 29%–32%) with sensitivity 72% and specificity 72%. Applied to whole brain, the global specificity increased to 88% with no change in sensitivity. This compared with sensitivity 66% and specificity 72% within the TTP lesion for absolute CBV <1.8% and specificity 75% in the whole brain (full results, Supplemental Table II).
Baseline vessel occlusion did not alter the optimal threshold (relative CBF 30% versus 31%).

**Applying the Thresholds**

Visual inspection corroborated that CBF thresholds had better agreement with the diffusion lesion than CBV (Figure 3). The higher AUC for CBF resulted from a reduced volume of “false-positive” subthreshold white matter at any given level of sensitivity. In the contralateral hemisphere, this false-positive volume was significantly lower for relative CBF than relative CBV (median, 6.2 mL versus 35.5 mL; \(P<0.0001\)). The performance of a global threshold for relative CBF and CBV was superior to their absolute counterparts. It was visually evident that this resulted from random variation in scaling of the absolute parameters due to VOF and arterial input function partial voluming in these relatively narrow slabs. Normalization to the contralateral mean to produce relative CBF or CBV corrected for these scaling errors.

The main “false-positive” errors occurred in regions of noninfarcted white matter. The volume of false-positive brain with relative CBF <31% in the contralateral hemisphere had a significant inverse correlation with the intensity of the contrast bolus as assessed by the peak VOF intensity in Hounsfield units (\(r=-0.30, P=0.003\)). False-positive low CBF was also prominent in regions of leukoaraiosis (Figure 4). There were also false-negative regions, usually surrounding large vessels (eg, sylvian fissure; Figure 3) where the “halo” of partial voluming falsely elevates CBF and masks regions of infarction that are evident on diffusion MRI. Another cause of heterogeneity in the data was temporal truncation of the contrast bolus. Truncation occurred to some degree in 30 of 98 slabs. Although there was essentially no change in global AUC, the resultant underestimation of CBV and CBF led to a shift in optimal threshold in these patients (Table 2). As a result, the volume of infarct core would be overestimated if the standard optimal threshold were applied to truncated data.

**Discussion**

This study has demonstrated that relative CBF is the optimal parameter to determine irreversible infarction using CTP, performing significantly better than CBV and in contrast to the main previous work in this area. Relative CBF remains consistently superior across a range of postprocessing conditions, although the quality of infarct core prediction is clearly dependent on factors such as degree of smoothing and the specific deconvolution algorithm used. Using our customizable processing pipeline, we found an optimal threshold of <31% of the contralateral mean CBF, although alternative software with different processing may require a different threshold. Our data highlight the potential variability in infarct core estimates that may result from the current wide variety in postprocessing algorithms used by different CT manufacturers and independent software vendors. Clinical
trials using CTP selection therefore need to use the same software across all sites.

The key issue in this analysis was consistency in performance of a chosen threshold across a broad cohort of patients. For this purpose, relative CBF performed significantly better than absolute CBF. This occurred due to random variability in the scaling factors applied due to partial volumed VOF and arterial input function available for selection in these relatively thin (24 mm) slabs of brain. The performance improvement in AUC using CBF rather than CBV corresponded to a visually apparent reduction in false positive regions in white matter. Our finding may differ from the previous data,8 which favored absolute CBV due to the nature of the ROC analysis used. We analyzed the full range of CBF and CBV values, whereas Wintermark et al restricted the analysis on the basis of previously published values to relative CBF 40% to 90% and absolute CBV 0.5% to 3.5%. Our optimal threshold of relative CBF was below this arbitrary range. Furthermore, our sample is twice the size of the previous analysis (54 patients with acute diffusion-weighted imaging versus 25 patients). In our analysis, the sSVD (delay-sensitive) deconvolution used by Wintermark et al performed at least as well

### Table 1. Global Optimal Thresholds (Determined by Maximizing Youden Index) for Different CT Perfusion Maps to Maximize Correspondence With the Acute DWI Lesion

<table>
<thead>
<tr>
<th>Degree of Smoothing</th>
<th>Tmax,* sec</th>
<th>TTP, sec</th>
<th>Absolute CBF,* mL/100 g/min</th>
<th>Relative CBF,* %</th>
<th>Absolute CBV, mL/100 g</th>
<th>Relative CBV, %</th>
<th>MTT,* sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.4</td>
<td>9.0</td>
<td>24</td>
<td>44</td>
<td>2.2</td>
<td>58</td>
<td>16.6</td>
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<td>2</td>
<td>10.2</td>
<td>9.1</td>
<td>19</td>
<td>37</td>
<td>1.9</td>
<td>60</td>
<td>14.5</td>
</tr>
<tr>
<td>4</td>
<td>8.9</td>
<td>9.5</td>
<td>15</td>
<td>32</td>
<td>1.9</td>
<td>56</td>
<td>13.7</td>
</tr>
<tr>
<td>6</td>
<td>8.9</td>
<td>8.8</td>
<td>15</td>
<td>31</td>
<td>1.8</td>
<td>58</td>
<td>13.0</td>
</tr>
<tr>
<td>8</td>
<td>8.9</td>
<td>8.8</td>
<td>15</td>
<td>30</td>
<td>1.9</td>
<td>59</td>
<td>12.8</td>
</tr>
<tr>
<td>10</td>
<td>8.9</td>
<td>8.8</td>
<td>15</td>
<td>30</td>
<td>2.0</td>
<td>60</td>
<td>13.2</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; Tmax, time to peak of the deconvolved tissue residue function; TTP, time to peak; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time.

* sSVD maps.
CBF than CBV.17,18 Our results go some way to explaining methodology have also reported better performance with studies using concurrent diffusion MRI lesions and ROC region in the remainder, VOF truncation was associated with slow bolus transit are frequently encountered. In our sample, this is relatively common in clinical practice because acquisition unless suboptimal acquisition reduces signal to noise CBV, cerebral blood volume; MTT, mean transit time; AUC, area under the curve.

There remain several important factors that limit the accuracy of CTP in identifying infarct core. Normal white matter has considerably lower CBF than gray matter.19–22 The threshold of <31% relative CBF is generally below the level of CBF in normal white matter. Therefore, the gray–white CBF gradient does not necessarily impact infarct core delineation unless suboptimal acquisition reduces signal to noise (already lower in CT compared with MR perfusion), leading to failure to detect flow in regions of normal white matter. We have identified that contrast bolus intensity is one determinant of the volume of “false-positive” white matter below the optimal threshold for defining infarction. In addition, it is well recognized that patients with leukoaraiosis have low CBF in affected regions.23,24 In this study, it was apparent that leukoaraiosis led to “false-positive” regions with CBF below the optimal threshold for infarction. These regions are often symmetrical and periventricular and identification may be aided by assessing the noncontrast CT and CTP in parallel. Another technical pitfall is failure to capture the entire transit of the contrast bolus, which shifts the optimal threshold and, if unrecognized, will overestimate the volume of infarct core. This is relatively common in clinical practice because acquisition length is limited by concerns about excessive radiation exposure and patients with poor cardiac output and resultant slow bolus transit are frequently encountered. In our sample, 30% of acquisitions had major truncation of the venous outflow curve and, although we cannot exclude minor truncation of the tissue concentration curve within the infarcted region in the remainder, VOF truncation was associated with a shift in optimal threshold. A longer acquisition time (at least 70–90 seconds) should be considered to avoid this issue, as recommended by expert consensus.25

Use of CTP thresholds is also subject to “false-negative” errors. We have observed that this is generally surrounding large blood vessels in which the partial voluming of very high CBF/CBV may mask regions of infarction that would be evident using diffusion MRI. This particularly occurs in the sylvian fissure where middle cerebral artery branches sometimes obscure assessment of the insular cortex. Eliminating vascular pixels can be used to mask out vessels. This does not, however, prevent the partial voluming effects in adjacent brain and cannot distinguish whether these regions are infarcted.

CT technology continues to evolve. Our data were acquired on a 16-slice scanner, which has been superseded in many institutions by machines with significantly greater slab coverage. Although this is a potential limitation, there is no reason to suspect that the performance of individual perfusion parameters in 16-slice data would differ using current state-of-the-art CT. The greater brain coverage of these newer scanners does, however, lead to advantages in analysis of mismatch between perfusion lesion and infarct core, which is a potential future avenue for research. A strength of this study is the use of sequential CT and MRI data, which overcomes much of the variability introduced by reperfusion, infarct edema, and atrophy that complicates interpretation of studies based on follow-up infarction.

This study has demonstrated that relative CBF is the optimal parameter for identifying infarct core using CTP. We have demonstrated ways in which different processing pathways alter the optimal thresholds and some of the potential pitfalls that lead to false-positive and false-negative regions. Accurately identifying infarct core is a crucial parameter in the estimation of the potentially salvageable brain tissue in the ischemic penumbra. Future work on optimizing smoothing algorithms and managing leukoaraiosis and vessel contamination will hopefully lead to improved sensitivity and specificity.
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Disclosures
None.

References
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Supplementary methods:

ROC analysis:

ROC analysis was performed to assess the discriminative power of each perfusion parameter with respect to the co-registered concurrent DWI lesion as gold standard using Matlab following the method of Christensen et al. Analysis was restricted to voxels within the manually outlined TTP perfusion lesion. This was based on the rationale that the optimal threshold should distinguish abnormally perfused tissue without infarction from true infarct core. Regions of diffusion lesion that fell outside the visible perfusion lesion (due to reperfusion or minor co-registration inaccuracy) were excluded from the analysis. For each map we defined a range of comprehensive thresholds, from the minimum value to the maximum value found in that map type. Then we generated functions of sensitivity and specificity for the classifier (DWI positive/negative) along these thresholds. These individual sensitivity and specificity functions were subsequently averaged to form global sensitivity and specificity functions which were used to construct a global ROC curve for DWI status at each threshold. The AUC of this global curve reflects the ability of a common threshold of the parameter to correspond to the diffusion lesion across all patients. This avoids the situation where excellent AUC values may be achieved in different patients but with different optimal thresholds which prevents prospective application of the derived threshold to other patients. Optimal thresholds from the global AUC curve were determined by maximizing Youden's index (=sensitivity+specificity-1). If these optimal thresholds were applied to all maps in this analysis, the mean sensitivity and specificity across patients would be exactly as identified on the global
ROC curve. Confidence intervals (CI) for the global AUC statistics were derived by bootstrapping (10,000 random samples with replacement). To formally test the difference between relative CBF and absolute CBV AUC values, we calculated AUC for both parameters in each of 10,000 bootstrap samples. The distribution of differences between these paired AUC values for relative CBF and absolute CBV in each bootstrap was tested against 0 using a sign test. The performance difference between CBF and CBV was also assessed by measuring sensitivity, specificity, positive/negative predictive values and the median volume of contralateral false positive tissue below threshold (Wilcoxon).
**Supplementary Table S1**: Comparison of AUC and optimal thresholds from ROC analysis using perfusion maps derived by circular (oSVD) versus standard (sSVD) deconvolution. Relative CBF performed best in both cases but in general AUC was slightly lower for circular than for standard deconvolution maps due to increased noise. Optimal thresholds for absolute and relative CBF (but not other parameters) shifted substantially as oSVD (delay-insensitive) deconvolution produces higher CBF estimates although notably this did not improve performance in assessing infarct core.

<table>
<thead>
<tr>
<th>CT perfusion map type*</th>
<th>Tmax</th>
<th>Absolute CBF</th>
<th>Relative CBF</th>
<th>Absolute CBV</th>
<th>Relative CBV</th>
<th>MTT</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>AUC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>sSVD</td>
<td>0.66</td>
<td>0.75</td>
<td>0.79</td>
<td>0.74</td>
<td>0.75</td>
<td>0.63</td>
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<tr>
<td>oSVD</td>
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<td>0.74</td>
<td>0.76</td>
<td>0.73</td>
<td>0.75</td>
<td>0.51</td>
</tr>
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<td>OOP</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>sSVD</td>
<td>8.9</td>
<td>15</td>
<td>31%</td>
<td>1.8</td>
<td>58%</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>sec</td>
<td>mL/100g/min</td>
<td>mL/100g</td>
<td>sec</td>
<td></td>
<td></td>
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<tr>
<td>oSVD</td>
<td>10.3</td>
<td>25†</td>
<td>40%†</td>
<td>1.7</td>
<td>57%</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>sec</td>
<td>mL/100g/min</td>
<td>mL/100g</td>
<td>sec</td>
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*6 pixel width Gaussian smoothing kernel, † p<0.05 for difference in OOP
Supplementary Table S2: Comparison of sensitivity, specificity, positive and negative predictive value of global optimal thresholds from ROC both within the manually outlined TTP perfusion lesion and in whole brain. Note the larger difference in specificity between relative CBF and absolute CBV when applied to whole brain due to false positive regions in normal white matter.

<table>
<thead>
<tr>
<th>Parameter/Threshold*</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>Relative CBF&lt;31%</td>
<td>72%</td>
<td>73%</td>
<td>56%</td>
<td>76%</td>
<td>72%</td>
<td>88%</td>
<td>37%</td>
<td>97%</td>
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<tr>
<td>Absolute CBF &lt;15ml/100g/min</td>
<td>70%</td>
<td>69%</td>
<td>54%</td>
<td>74%</td>
<td>69%</td>
<td>85%</td>
<td>35%</td>
<td>97%</td>
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<tr>
<td>Relative CBV &lt;58%</td>
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<td>69%</td>
<td>51%</td>
<td>70%</td>
<td>69%</td>
<td>73%</td>
<td>17%</td>
<td>95%</td>
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<tr>
<td>Absolute CBV &lt;1.8%</td>
<td>66%</td>
<td>72%</td>
<td>53%</td>
<td>70%</td>
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<td>75%</td>
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<td>Relative TTP &gt;8.8sec</td>
<td>56%</td>
<td>74%</td>
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<td>96%</td>
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<td>74%</td>
<td>54%</td>
<td>68%</td>
<td>55%</td>
<td>89%</td>
<td>48%</td>
<td>95%</td>
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<tr>
<td>MTT &gt; 13.0sec</td>
<td>55%</td>
<td>64%</td>
<td>48%</td>
<td>65%</td>
<td>55%</td>
<td>86%</td>
<td>39%</td>
<td>95%</td>
</tr>
</tbody>
</table>

*sSVD maps, 6 pixel width Gaussian smoothing kernel
Supplemental references:

   Comparison of 10 perfusion-MRI parameters in 97 sub-6-hour stroke patients 
   using voxel-based receiver-operating-characteristics analysis. *Stroke.* 
   2009;40:2055-2061