CT Cerebral Blood Flow Maps Optimally Correlate With Admission Diffusion-Weighted Imaging in Acute Stroke but Thresholds Vary by Postprocessing Platform

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Background and Purpose—Admission infarct core lesion size is an important determinant of management and outcome in acute (<9 hours) stroke. Our purposes were to: (1) determine the optimal CT perfusion parameter to define infarct core using various postprocessing platforms; and (2) establish the degree of variability in threshold values between these different platforms.

Methods—We evaluated 48 consecutive cases with vessel occlusion and admission CT perfusion and diffusion-weighted imaging within 3 hours of each other. CT perfusion was acquired with a “second-generation” 66-second biphasic cine protocol and postprocessed using “standard” (from 2 vendors, “A-std” and “B-std”) and “delay-corrected” (from 1 vendor, “A-dc”) commercial software. Receiver operating characteristic curve analysis was performed comparing each CT perfusion parameter—both absolute and normalized to the contralateral uninvolved hemisphere—between infarcted and noninfarcted regions as defined by coregistered diffusion-weighted imaging.

Results—Cerebral blood flow had the highest accuracy (receiver operating characteristic area under the curve) for all 3 platforms (P<0.01). The maximal areas under the curve for each parameter were: absolute cerebral blood flow 0.88, cerebral blood volume 0.81, and mean transit time 0.82 and relative Cerebral blood flow 0.88, cerebral blood volume 0.83, and mean transit time 0.82. Optimal receiver operating characteristic operating point thresholds varied significantly between different platforms (Friedman test, P<0.01).

Conclusions—Admission absolute and normalized “second-generation” cine acquired CT cerebral blood flow lesion volumes correlate more closely with diffusion-weighted imaging-defined infarct core than do those of CT cerebral blood volume or mean transit time. Although limited availability of diffusion-weighted imaging for some patients creates impetus to develop alternative methods of estimating core, the marked variability in quantification among different postprocessing software limits generalizability of parameter map thresholds between platforms. (Stroke. 2011;42:1923-1928.)

Key Words: acute stroke ■ cerebral blood flow ■ cerebral blood volume ■ CT perfusion

There is interest in studying core and penumbra to investigate whether they improve clinical outcomes from the use of thrombolytic therapy.1,2 Diffusion-weighted imaging (DWI) is widely accepted as the de facto clinical reference standard for the core, but widespread implementation of MRI is hindered by availability as well as technical and safety limitations.3 Noncontrast CT is currently the standard of care to exclude hemorrhage before thrombolytic therapy, yet sensitivity for early infarction is poor.4 A reliable “DWI-like” CT measure of infarct core could therefore be of interest.

CT perfusion (CTP) is widely available and acquisition times are rapid.5 The most common and robust method to calculate CTP parameters is singular value decomposition deconvolution.5 Potential sources of variability in this method include placement of the venous normalization region of interest, computational differences in algorithms, and the delay between the arterial and tissue time-density curves (common in patients with acute ischemic stroke).5–8 Hence, different postprocessing software platforms have the potential to result in different values for CTP parameters.

Although multiple studies have been published to determine the CTP parameter maps and corresponding threshold values that optimally define infarct core, systematic technical differences in both acquisition and postprocessing algorithms
between different platforms limit their generalizability and reproducibility. Most were not only vendor-dependent, but were performed using “first-generation” CTP acquisition protocols and postprocessing software—specifically 45-second acquisitions and early versions of deconvolution algorithms—which might exaggerate the magnitude of the CT cerebral blood volume (CBV) lesion size if there is truncation of the tissue time-density curves. Our purposes were to: (1) determine the optimal CTP parameter to define the infarct core using various postprocessing platforms (compared with a DWI reference standard, and using a more current “second-generation” 66-second biphasic cine acquisition protocol); and (2) establish the degree of variability in the optimal threshold values between these different platforms.

**Methods**

**Patient Selection**

We reviewed the records of all consecutive patients admitted with the diagnosis of acute ischemic stroke within 9 hours of symptom onset from December 2006 to April 2008. We identified 98 patients with acute ischemic stroke in the anterior circulation who had biphasic CTP and DWI obtained within 3 hours of one another. Cases were excluded for no visible vessel occlusion (n=28), punctate or no apparent DWI lesion (n=10), or poor quality DWI (n=5) or CTP (n=7) acquisition due to motion or truncated arterial or venous density curves, yielding 48 cases for analysis. The study received Institutional Review Board approval and was Health Insurance Portability and Accountability Act-compliant.

**Imaging Acquisition**

CTP was performed on a multislice helical scanner (64-slice LightSpeed GE Medical Systems, Milwaukee, WI) as a 66-second biphasic cine series beginning 5 seconds after power injection of 40 mL of contrast at 7 mL/s, which contains 755 mg/mL of iopamidol (Isovue Multipack-370; Bracco Diagnostics Inc, Princeton, NJ). Image acquisition was every half second for the first 40 seconds, which was followed by a 2-second pause and 8 more acquisitions every 3 seconds. Imaging parameters were 80 kVp, 200 mAs, and 1-second rotation time. Coverage consisted of 2 slabs positioned parallel and superior to the orbital roof. Each slab consisted of 8 slices of 5-mm thickness.

DWI was obtained on a 1.5-Tesla Signa scanner (GE Medical Systems) using single shot, spin-echo echoplanar imaging. High b-value images (b=1000 s/mm²) were acquired in 6 different gradient directions in addition to a single low b-value (b=0 s/mm²) image. Other parameters were: repetition time of 5000 ms, time to echo of 90 to 100 ms, field of view of 22×22 cm, image matrix of 128×128, slice thickness of 5 mm with a 1-mm gap, and 5 signal averages.

**Image Analysis**

CTP maps were postprocessed using delay-corrected software (CTP5 “A-de”; GE Healthcare) and 2 standard deconvolution software packages (CTP3 “A-std”; GE Healthcare; and Brain Perfusion “B-std”; Philips). DWI images were coregistered to CTP data using a fully automated rigid method (CTI Molecular Imaging-Reveal-MVS 6.2; Mirada Solution Ltd). The images were manually adjusted in case of unsatisfactory coregistration.

Visually detected DWI lesions were semiautomatically segmented, selecting only the slice with the largest area of the infarction before the CTP analysis (Figure 1A). A mirrored region of interest for normalization of the absolute voxel values was placed over the contralateral uninvolved hemisphere. Temporally averaged cine CTP images were served for segmentation of gray matter, white matter, and basal ganglia (Figure 1B). All regions of interest were transposed onto the perfusion maps, and the voxel values were recorded using a commercial analysis program (Analyze 7.0; AnalyzeDirect, Mayo Clinic, Rochester, MN).

The normalized perfusion parameter values were calculated in 3 ways: first, by dividing each voxel value by the mean of the contralateral normal hemisphere voxel values; second, by dividing each voxel value by the mean contralateral reference region of interest value; and third, by dividing each voxel value in gray matter, white matter, and basal ganglia by the mean of the corresponding contralateral normal gray matter, white matter, and basal ganglia values. Because there was no significant difference among these 3 normalization approaches, for simplicity, we report only the results using the first method.

**Statistics**

For each CTP parameter map, both relative and absolute receiver operating characteristic (ROC) curves depicting the sensitivity/specificity for distinguishing core voxels from noncore voxels were generated from the pooled voxel values for all patients. Thresholds were then calculated as the optimum ROC operating point with equally attributed weights to specificity and sensitivity; overall accuracy was estimated as the area under the curve (AUC).

Because the millions of voxels contributing to the pooled ROC analysis could result in a statistically significant but not necessarily clinically meaningful comparison between the parameters being tested, a patient-based comparison of the individual ROC AUCs was

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**Figure 1.** Sample image segmentation methodology for right hemispheric infarct.

A, Admission diffusion-weighted imaging (DWI) lesion (black outline). A mirrored region of interest (white outline) over the contralateral uninvolved hemisphere served for normalization of the absolute voxel values. B, Temporally averaged cine CT perfusion (CTP) image served as a template for the segmentation of gray matter, white matter, and basal ganglia (black outline).
performed to compare relative cerebral blood flow (CBF), CBV, and CBV*CBF from each software package using a paired Wilcoxon analysis. Optimal ROC operating point thresholds for each parameter were also compared to assess for significant difference using a nonparametric paired comparison (Friedman test) between different software package maps. STATA 10 (Stata, College Station, TX) software was used to perform the statistical analysis.

### Results

Of the 48 patients included in the analysis, 22 (46%) were male and mean age was 71.6 years (range, 26 to 97 years; SD, 14). Other important demographics were as follows (median [interquartile range]): admission National Institutes of Health Stroke Scale 13 (8 to 20), symptom onset to CTP time 4.1 hour (2 to 5.3 hours), and CTP to DWI interval 34 minutes (28 to 43 minutes). Atrial fibrillation was present in 15 (31%) patients, all of whom had concomitant major intracranial vessel occlusions. Vessel occlusion was on the left in 29 (60%) patients. Location of occlusions were as follows: 4 (8%) internal carotid artery and M1 segment of the middle cerebral artery; 4 (8%) internal carotid artery, M1, and M2; 3 (6%) internal carotid artery, M1 and M2, and anterior cerebral artery; 7 (15%) M1 only; 9 (19%) M1 and M2; 15 (31%) M2 only; 1 (2%) M2 and M3; 3 (6%) M3 only; 1 (2%) M1, M2, and anterior cerebral artery; and 1 (2%) M1 and anterior cerebral artery involved.

More than 2.5 million voxels were analyzed, approximately 250,000 of which corresponded to regions of restricted diffusion on DWI. Mean DWI lesion volume on the selected slices was 5.84 mL (range, 0.6 to 20.6; SD, 4.68).

For each of the 3 software packages, the relative and absolute CBF had higher AUCs for determination of core than CBV and mean transit time (Table 1, voxel-based analysis). The optimal thresholds for relative and absolute CBF and CBV varied substantially accordingly across software packages. The optimal absolute CBF thresholds were 4.7, 5.4, and 10 mL/100 g/min using A-std, A-dc, and B-std software, respectively. The corresponding optimal normalized thresholds were 84%, 72%, and 68% reduction in CBF, respectively. AUC, thresholds, sensitivity, and specificity are reported in Supplemental Table I (http://stroke.ahajournals.org) for the 3 software packages for absolute and relative CBF, CBV, mean transit time, and CBV*CBF for the whole brain and for segmented gray matter, white matter, and basal ganglia. All pairwise comparisons between the relative CBF (rCBF) and relative CBV (rCBV) AUCs for each software were statistically significant (P<0.01; Table 2, patient-based analysis). Comparisons between the rCBF and rCBV*CBF AUCs were not statistically significant, except for software “B-std” (P<0.01). rCBF using software “A-std” had the highest AUC (P<0.01). Optimal ROC operating point thresholds varied significantly across the different platforms (P<0.01; Figure 2).

Figure 3 shows sample overlays for infarction core using the optimal operating point thresholds for absolute CBV and CBF for all 3 software packages.

### Discussion

We have shown that: (1) CBF is the optimal CTP parameter for estimating DWI-defined infarct core, exceeding CT-CBV.

| Table 2. Patient-Based Comparison of the Relative CTP Parameter ROC-AUCs and Postprocessing Software Platforms |
|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Software | Parameter | Median (95% CI)* | Comparison Software | Comparison Parameter | Median (95% CI)* | Wilcoxon P |
| A-std   | rCBV      | 0.81 (0.78–0.83) | A-std | rCBF      | 0.86 (0.83–0.89) | <0.01 |
| A-dc    | rCBV      | 0.76 (0.72–0.78) | A-dc  | rCBF      | 0.83 (0.79–0.87) | <0.01 |
| B-std   | rCBV      | 0.73 (0.70–0.77) | B-std | rCBF      | 0.80 (0.74–0.83) | <0.01 |
| A-std   | rCBF      | 0.86 (0.83–0.89) | A-std | rCBV*CBF  | 0.86 (0.82–0.88) | 0.49  |
| A-dc    | rCBF      | 0.83 (0.79–0.87) | A-dc  | rCBV*CBF  | 0.83 (0.79–0.87) | 0.82  |
| B-std   | rCBF      | 0.80 (0.74–0.83) | B-std | rCBV*CBF  | 0.80 (0.75–0.85) | <0.01 |
| A-std   | rCBF      | 0.86 (0.83–0.89) | A-std | rCBF      | 0.83 (0.79–0.87) | <0.01 |
| A-dc    | rCBF      | 0.86 (0.83–0.89) | B-std | rCBF      | 0.80 (0.74–0.83) | <0.01 |
| B-std   | rCBF      | 0.83 (0.79–0.87) | B-std | rCBF      | 0.80 (0.74–0.83) | <0.01 |

*Confidence interval for median.
in accuracy; and that (2) significant variation exists between the optimal parameter threshold values for different postprocessing platforms. Strengths of our study include the use of advanced “second-generation” CTP acquisition protocols that are sufficiently long to permit the complete transit of intravenous contrast through the brain (thus resulting in more physiologically correct perfusion maps), a coregistered CTP-DWI voxel-based ROC analysis, comparison of multiple vendor software and postprocessing platforms, and inclusion of heterogeneous patients with hemodynamic irregularities from both large vessel occlusion and atrial fibrillation. These methodological considerations may explain much of the difference between our results and those of earlier reports and highlight the significant variability in optimal parameter thresholds between different platforms. Despite the variability in our reported thresholds, they remain within the range of prior meta-analyses, and our conclusion that CBF is nominally more accurate than CBV in delineating the core appears to be generalizable across platforms.

Our use of DWI as a reference standard, rather than follow-up infarct size in patients with early complete recanalization, may also have contributed to quantitative differ-

Figure 2. A, Sample receiver operating characteristic (ROC) curves for CT perfusion (CTP) delineation of diffusion-weighted imaging (DWI)-defined core using “A-dc” postprocessing software (absolute parameter values only; red, CBF; purple, CBV*CBF; green, CBV; and blue, MTT). B, Bar graph of area under curve (AUC), sensitivity, and specificity (Y-axis) at the optimal ROC operating point for each CTP parameter and postprocessing platform (“A-std,” “A-dc,” and “B-std”; X-axis) for delineation of core (r indicates relative). CBF indicates cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; std, standard; dc, delay-corrected.

Figure 3. Sample optimal absolute CBF and CBV pixel thresholds (red overlay applied to the temporally averaged cine CTP template) for right hemispheric stroke. A, Admission DWI (left) and temporally averaged CTP template (right); (B) software “A-std”: CBV (left), CBF (right); (C) Software “A-dc”: CBV (left), CBF (right); (D) software “B-std”: CBV (left), CBF (right). CBF indicates cerebral blood flow; CBV, cerebral blood volume; CTP, CT perfusion; DWI, diffusion-weighted imaging.
ences between our results and prior studies, including that found higher CBF/CBV thresholds using the “A-std” software. Technical differences in postprocessing (such as our use of the “vessel exclusion off” clinical default mode) were likely also important. Although DWI lacks perfect specificity for the infarct core, it is both highly accurate and widely accepted in research and clinical care. With regard to our use of a more lengthy 66-second CTP acquisition time, rather than a “first-generation” time of 45 seconds, there is recent consensus that acquisition should be sufficiently long to permit the full wash-in and wash-out of contrast so that complete, nontruncated time-density tissue curves can be obtained (crucial if concurrent permeability imaging is also performed). Short imaging times can lead to truncation of the tissue time-density curves in regions with severe hemodynamic derangement due to severe vascular stenosis/occlusion and/or atrial fibrillation, which can distort the—typically vendor-dependent—CTP parameter value calculations. Indeed, our conclusion regarding the accuracy of CBF versus CBV in determining the core is supported by the fact that calculation of CBV is typically more sensitive to time-density curve truncation than is CBF and by previous work suggesting that CBV lesion size can be overestimated in the setting of marked hemodynamic derangement.

That CBV has greater variability than CBF in delineating the core is also consistent with the established hemodynamic alterations accompanying ischemia. Most relevant of these is luxury perfusion—CBV hyperemia of penumbra or recanalized core—that occurs not infrequently in maximally vaso-dilated, critically ischemic tissue.

Our study highlights several technical limitations to the interpretation of CTP data. First, it is clear that the parameter thresholds obtained using one CTP postprocessing platform may not be generalizable to other CTP methodologies. Currently, there is no standardization of CTP postprocessing software across different vendors, different reconstruction algorithms, or even different versions of the same software package for a given vendor. Further variability in absolute quantification of flow values can be introduced by volume averaging effects in selecting the venous outflow region of interest for normalization during CTP map construction. Indeed, variability in quantitation of perfusion parameter values has recently been identified in a simulated data set comparing delay-sensitive to delay-insensitive deconvolution techniques.

Unlike most prior investigations of CTP thresholds for infarct core, we minimized bias by using a more objective, voxel—rather than regional—based image analysis method. We determined the optimal core threshold values for each CTP parameter by transposing the segmented DWI core lesion directly onto the coregistered CTP maps and performing ROC curve analyses to determine the optimal operating points for distinguishing infarcted from noninfarcted voxels. Hence, subjective differences in image display such as gray scale, window/level settings, and pixel conspicuity, which might introduce subjectivity in manual segmentation, were eliminated.

A limitation inherent in all perfusion studies of acute ischemia is that they represent a “snapshot” in time, and that—specifically for very early times postictus (<3 hours)—thresholds for irreversible ischemic damage may vary. Unfortunately, our study lacked sufficient patients to stratify our data by time postictus. Moreover, although we could not control for the potential confounding effects of reperfusion just before scanning on our threshold analysis, there were no imaging findings (such as partially recanalized vessels on CT angiography) to suggest this.

Conclusions
Our study has demonstrated that appropriately thresholded CT-CBF maps, more so than CT-CBV, optimally delineate DWI-defined infarct core but that the specific thresholds vary by postprocessing software version and vendor (approximately 70% to 85% reduction in CBF). Although CTP imaging cannot replace DWI for the accurate delineation of infarct core, CTP is likely to be the best alternative modality—more accurate than unenhanced CT or CT angiography source images—for making this clinically important assessment in patients for whom MRI cannot be obtained.

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References


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## SUPPLEMENTAL MATERIAL

### Online Supplement Table 1: ROC Analysis at the Operating Point for Pooled Voxel-Based Thresholded CTP Parameter Map Assessment of Infarct Core

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</table>

AUC: Area Under the ROC Curve; T: Threshold; SN: Sensitivity; SP: Specificity; r: relative.