Perfusion CT in Acute Stroke: A Comprehensive Analysis of Infarct and Penumbra[1]

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Purpose: To perform a large-scale systematic comparison of the accuracy of all commonly used perfusion computed tomography (CT) data postprocessing methods in the definition of infarct core and penumbra in acute stroke.

Materials and Methods: The collection of data for this study was approved by the institutional ethics committee, and all patients gave informed consent. Three hundred fourteen patients with hemispheric ischemia underwent perfusion CT within 6 hours of stroke symptom onset and magnetic resonance (MR) imaging at 24 hours. CT perfusion maps were generated by using six different postprocessing methods. Pixel-based analysis was used to calculate sensitivity and specificity of different perfusion CT thresholds for the penumbra and infarct core with each postprocessing method, and receiver operator characteristic (ROC) curves were plotted. Area under the ROC curve (AUC) analysis was used to define the optimum threshold.

Results: Delay-corrected singular value deconvolution (SVD) with a delay time of more than 2 seconds most accurately defined the penumbra (AUC = 0.86, P = .046, mean volume difference between acute perfusion CT and 24-hour diffusion-weighted MR imaging = 1.7 mL). A double core threshold with a delay time of more than 2 seconds and cerebral blood flow less than 40% provided the most accurate definition of the infarct core (AUC = 0.86, P = .038). The other SVD measures (block circulant, nondelay corrected) were more accurate than non-SVD methods.

Conclusion: This study has shown that there is marked variability in penumbra and infarct prediction among various deconvolution techniques and highlights the need for standardization of perfusion CT in stroke.

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Perfusion computed tomography (CT) has shown considerable promise with regard to the selection of patients with ischemic stroke who can benefit from treatment with thrombolysis (1). Although perfusion CT has been used to identify critically hypoperfused tissue, including the infarct core and penumbra (2), and is fast and widely available, it has not yet gained widespread acceptance in the selection of patients for acute reperfusion therapies (3,4). One major reason is the variability in the accuracy and reliability of perfusion CT owing to the different methods used to transform the raw perfusion data into measures of infarct core and penumbra (5). The variability brought about with different postprocessing methods is considerable and has led to confusion as to whether cerebral blood volume (CBV) or cerebral blood flow (CBF) is optimal for defining the acute infarct core (2). Moreover, the variability of postprocessing methods leads to considerable differences in the CBV or CBF thresholds used to measure the acute infarct core or penumbra volumetrically. The aim of this study was to perform a large-scale systematic comparison of the accuracy of all commonly used perfusion CT data postprocessing methods in the definition of infarct core and penumbra in acute stroke.

Advances in Knowledge

- CT perfusion thresholds for defining the acute infarct core and penumbra varied significantly according to the various deconvolution algorithms used across various vendors.
- The acute infarct core can be better defined by limiting the volume to within the perfusion lesion for deconvolution-based postprocessing.
- Lesion volume at diffusion-weighted MR imaging did not change over time if a patient showed major reperfusion at 24 hours.

Materials and Methods

Patients

A cohort of 507 patients presenting with hemispheric ischemia between 2005 and 2011 were recruited by neurologists and studied retrospectively (M.P., N.S., and C.L., stroke imaging neurologists with >10 years of experience). Patients underwent imaging with multimodal CT as a baseline examination (within 6 hours of symptom onset) and with a follow-up magnetic resonance (MR) imaging stroke sequence at 24 hours. A subgroup of these patients also underwent acute MR imaging within an hour of the initial perfusion CT study if they were clinically stable and had no contraindications to MR imaging. Clinical stroke severity was assessed by experienced stroke neurologists or stroke research nurses immediately before the two imaging time points by using the National Institutes of Health Stroke Scale. Eligible patients were treated with intravenous thrombolysis according to standard guidelines. No patient underwent intra-arterial clot retrieval because this service was not available at our institution. Patients were included in this study if ischemic stroke was diagnosed according to hypoperfusion at acute perfusion imaging. Patients were excluded if they had hemorrhagic stroke (89 patients, 17%), contraindications to MR imaging (51 patients, 10%), incomplete data (17 patients, 3%), or poor data quality, including excessive motion at imaging (36 patients, 7%), leaving a total of 316 patients for analysis. Other analyses have previously been performed with subsets of this data set (1,6). The collection of data for this study was approved by the institutional ethics committee, and all patients gave informed consent.

Implication for Patient Care

- With use of these methods, perfusion imaging thresholds can be optimized for defining the volume of the acute infarct core or penumbra when using perfusion CT in patients with acute ischemic stroke; in addition, for future trials it will be important to use either a single form of deconvolution to define acute tissue pathophysiology or the optimal thresholds for each scanner.

Imaging

Whole-brain unenhanced CT was followed by perfusion CT, which comprised two 60-second series (64-section Philips Brilliance; Philips, Cleveland, Ohio). Perfusion CT was performed with intravenous injection of a bolus of contrast material (40 mL of Ultravist 370; Bayer Healthcare, Berlin, Germany) at a rate of 6 mL/sec, with 45 time points acquired each 1.33 seconds. Each perfusion series covered a 24–40-mm section acquired as four adjacent 6-mm sections. The first section was at the level of the basal ganglia and/or internal capsule, and the second was placed 6 mm toward the vertex to avoid overlap. CT angiography was performed after perfusion CT, with acquisition from the aortic arch to the top of the lateral ventricles (7).

MR imaging was performed with a 1.5-T MR unit (Avanto; Siemens, Erlangen, Germany). The stroke MR imaging protocol included an axial isotropic diffusion-weighted echo-planar spin-echo sequence, time-of-flight MR

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Abbreviations:
AIF = arterial input function
AUC = area under the ROC curve
CBF = cerebral blood flow
CBV = cerebral blood volume
CI = confidence interval
MTT = mean transit time
ROC = receiver operating characteristic
SVD = singular value deconvolution
T_{max} = time to peak of the residual function

Author contributions:
Guarantors of integrity of entire study, A.B., C.L., M.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, A.B., C.L., N.S.; clinical studies, all authors; statistical analysis, A.B., C.L.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

angiography, and bolus-tracking perfusion-weighted imaging (8).

Perfusion Models

All CT perfusion maps were calculated with commercial software (MIStar; Apollo Medical Imaging Technology, Melbourne, Australia) (4). The software automatically performs motion correction and selects an arterial input function (AIF) from an unaffected artery (most often the anterior cerebral artery) and a venous output function from a large draining vein (the sagittal sinus). Chronic infarcts and/or gliosis and cerebrospinal fluid regions were automatically detected by a Hounsfield unit threshold and removed from the analysis. Areas of no blood flow were assigned maximal delay time and mean transit time (MTT) values. The perfusion lesion segmentation algorithm also uses a cluster analysis technique to remove small clusters of noisy pixels (6). Perfusion maps were then calculated by using six different methods biased on the original published methodology to approximate vendor software: maximum slope (Peters) model (9), partial deconvolution (used by Siemens), singular value deconvolution (SVD) (used by General Electric) (10), SVD with delay and dispersion correction (11), block-circulant deconvolution (used by Toshiba and Philips) (10), and a stroke-stenosis model (used by MIStar). All postprocessing techniques produced maps of CBF, CBV, and MTT. In addition, the maximum slope model produced a map of time to peak, the partial deconvolution, SVD, block-circulant deconvolution, and stroke-stenosis models produced a map of time to peak of the residual function (T_{max}), and SVD with delay correction produced a map of delay time. All imaging analyses were performed by an imaging research scientist with 3 years of experience (A.B.).The theoretical basis and assumptions in each model are detailed in Appendix E1 (online).

Patient Groups

Patients were divided into three groups according to changes in lesion volume between acute CT and MR imaging obtained at 24 hours with MTT of more than 145% (7,12), as follows: major reperfusion (>80% reperfusion at 24 hours), no reperfusion (<20% reperfusion at 24 hours), and partial reperfusion (20%–80% reperfusion at 24 hours). Patients with major reperfusion and acute diffusion-weighted MR images were used to define the acute infarct core (6). Patients with no reperfusion (<20%) have considerable infarct growth between acute CT and 24-hour diffusion-weighted MR imaging, and this volume difference is a reliable estimate of the extent of penumbra (6). Patients with partial reperfusion were excluded from further analyses because of the wide variability in infarct growth from acute CT to 24-hour diffusion-weighted imaging (these analyses were performed by A.B., a scientist with >3 years of experience, and M.P., a stroke imaging neurologist with >10 years of experience).

Image Analysis

CT perfusion maps were coregistered to the corresponding 24-hour and/or acute diffusion-weighted MR images (2,13). At acute and 24-hour diffusion-weighted MR imaging, lesions were automatically delineated on the basis of signal intensity thresholds of b = 1000 to rule out noise and false infarct. Next, the area of interest was transferred to the coregistered acute CT perfusion maps for analysis (see below). A range of relative (as a percentage of contralateral hemisphere) and absolute thresholds were then investigated at constant increments as shown in Table 1 (performed by A.B.) (14).

Table 1

CT Perfusion Thresholds Used to Define the Infarct Core and Penumbra

Parameter	Range	Increment
Relative CBV (%)	10–70	5
Absolute CBV (mL/100 g)	1–2.5	0.25
Relative CBF (%)	10–60	5
Absolute CBF (mL/100 g/min)	3–17	2
Delay (T_{max}) (sec)	2–10 over baseline	2
MTT (%)	150–300	50

Statistical Analyses

The acute infarct core was defined as the volume on the 24-hour diffusion-weighted MR image in patients with major reperfusion at 24 hours (or patients with an acute diffusion-weighted MR image). The acute perfusion lesion (core + penumbra) was defined by the volume on the 24-hour diffusion-weighted MR image in patients without major reperfusion.

Receiver operating characteristic (ROC) analysis was used to test the predictive performance of perfusion CT in relation to the infarct core at diffusion-weighted imaging. The diffusion-weighted image was considered to show the "true" lesion, and pixels falling within both the lesion seen on the diffusion-weighted MR image and the lesion seen on the perfusion CT scan were considered true positive. A diffusion-weighted MR imaging lesion (b = 1000 sec/mm^2) not within the perfusion CT lesion was considered true negative. Pixels within the lesion seen at perfusion CT but not within the lesion seen at diffusion-weighted MR imaging were considered false positive, and pixels within the lesion seen at diffusion-weighted MR imaging but not within the lesion seen at perfusion CT were considered false negative. Sensitivity (true-positive findings/[true positive + false negative findings]) was plotted against 1 − specificity (true negative findings/[true negative + false positive findings]) to generate the ROC curve for each perfusion map. Results for ROC analysis of each perfusion map are presented as the area under the ROC curve (AUC) and 95% confidence intervals (CIs).

To provide balance in the number of pixels being measured and prevent a very large true-negative value from overwhelming the ratio to false-positive findings in the calculation of specificity, only hemispheric (ischemic side) brain pixels were analyzed (rather than whole brain).

Once the most accurate perfusion CT lesion threshold had been identified on the basis of the highest AUC, two analyses were performed to derive infarct core thresholds: *(a)* The 24-hour diffusion-weighted MR image was compared with the acute perfusion CT scan

Table 2

Summary of Best Thresholds for Defining the Acute Infarct Core and Perfusion Lesion with the Six Deconvolution Methods

Model	Threshold	AUC	Sensitivity	Specificity	Mean Volume Error (cm^3)*	r^2
Maximum slope						
Infarct core	CBF <45%	0.69	0.46	0.89	−0.8 (−5.1, 7.3)	0.65
Perfusion lesion	MTT >145%	0.71	0.63	0.78	0.1 (−4.3, 4.5	0.76†
Double core threshold	CBF <40% and MTT >145%	0.67	0.53	0.77	−3.9 (−6.4, 2.5)	0.69†
Partial deconvolution						
Infarct core	CBF <10 mL/100 g/min	0.71	0.52	0.89	1.1 (−6.4, 7.4)	0.63
Perfusion lesion	Time to peak >4 sec	0.74	0.66	0.81	−1.3 (−1.9, 0.4)	0.68†
Double core threshold	CBF <7.5 mL/100 g/min and time to peak <4 sec	0.72	0.66	0.84	1.6 (1.1, 2.5)	0.7
SVD						
Infarct core	CBF <20 mL/100 g/min	0.70	0.7	0.69	−3.1 (−5.3, 0.7)	0.72
Perfusion lesion	T_{max} >6 sec	0.77	0.75	0.72	0.4 (−0.6, 1.1)	0.74†
Double core threshold	CBF: 7.5 mL/100 g/min and T_{max} >6 sec	0.74	0.56	0.92	0.5 (−0.3, 0.9)	0.74†
SVD with delay correction						
Infarct core	CBF <45%	0.77	0.75	0.79	1.99 (0.3, 3.6)	0.72
Perfusion lesion	Delay time >2 sec	0.86	0.83	0.82	1.7 (0.3, 2.6)	0.76†
Double core threshold	CBF <40% and delay time >2 sec	0.86	0.73	0.93	0.5 (−0.1, 0.9)	0.79†
Block-circulant deconvolution						
Infarct core	CBF <15 mL/100 g/min	0.73	0.73	0.77	4.7 (0.9, 8.7)	0.7
Perfusion lesion	Relative T_{max} >4 sec	0.72	0.82	0.62	2.2 (−0.5, 4.9)	0.72†
Double core threshold	CBF <15 mL/100 g/min and relative T_{max} >4 sec	0.79	0.75	0.79	1.1 (−0.5, 2.3)	0.71
Stroke-stenosis						
Infarct core	CBF <10 mL/100 g/min	0.75	0.84	0.65	3.6 (0.6, 5.4)	0.67
Perfusion lesion	CBF <20 mL/100 g/min	0.72	0.78	0.66	3.7 (0.9, 4.9)	0.75
Double core threshold	CBF <10% and CBF: 20 mL/100 g/min	0.72	0.82	0.63	1.6 (−0.3, 2.6)	0.73

Note.—Each deconvolution method has an optimal threshold; however, it is a consistent finding that CBF best defines the acute infarct core. In addition, when delay correction is applied, delay measures (T_{max} and delay time) are optimal at defining the acute perfusion lesion. When delay correction is not used, MTT is the optimal measure for defining the acute perfusion lesion, but this is less accurate.

* Numbers in parentheses are 95% CIs.

† $P < .05$.

in all patients with major reperfusion, and *(b)* the acute perfusion CT scan was compared with the acute diffusion-weighted MR image in the subgroup of patients who underwent concurrent acute MR imaging.

Analyses were undertaken to compare the accuracy of restricting the infarct core thresholds within the most accurate outer perfusion lesion thresholds (derived from the above "no reperfusion" threshold analysis), versus single-core threshold, for all six post-processing methods (1).

Clinical data were also analyzed by using paired *t* tests, corresponding Pearson correlation coefficient analysis, and simple linear regression. All statistical analyses were performed with software (SSPS 13.0; SSPS, Chicago, Ill) (by A.B.).

Results

From the total patient cohort of 316 patients, 146 (46%) had no significant reperfusion at 24 hours, 106 (34%) had major reperfusion, and 64 (20%) had partial reperfusion and were excluded from analysis. Sixty-seven patients (21%) underwent concurrent acute diffusion-weighted MR imaging within 1 hour of acute perfusion CT and were used to define the acute infarct core in the secondary analysis.

The median patient age was 70 years (range, 23–89 years), the median acute National Institutes of Health Stroke Scale score was 13 (range, 5–24), and the median time to end of perfusion CT was 162 minutes (interquartile range, 185–240 minutes). Intravenous thrombolysis was performed in 174 patients according to institutional guidelines. Of the patients who received thrombolysis, 82 (47%) had major reperfusion at follow-up imaging, 57 (33%) had no significant reperfusion, and 35 (20%) had partial reperfusion.

Maximum Slope Model

A relative CBF of less than 45% (AUC: 0.68; 95% CI: 0.64, 0.72) was the best single threshold for describing the acute infarct core. An MTT of more than 145% (AUC: 0.71; 95% CI: 0.67, 0.75) was the best threshold for describing the acute perfusion lesion. With use of the double core threshold approach, a relative CBF of less than 40% within a perfusion lesion with an MTT of more than 145% (AUC: 0.63; 95% CI: 0.61, 0.65) did not improve the accuracy of the single infarct

core threshold (CBF <45%, Table 2). A comprehensive analysis of the results is presented in Table E1 (online).

Partial Deconvolution

A relative CBF of less than 20% (AUC: 0.71; 95% CI: 0.65, 0.77) and an absolute CBF of less than 10 mL/100 g/min were the equal best descriptors of the acute infarct core. The acute perfusion lesion was most accurately described with an MTT greater than 155% (AUC: 0.73; 95% CI: 0.69, 0.77) or a time to peak greater than 4 seconds (AUC: 0.74; 95% CI: 0.70, 0.78). A double core threshold approach did not improve accuracy in defining the infarct core (Table 2). A comprehensive analysis of the results is presented in Table E2 (online).

SVD

An absolute CBF of less than 20 mL/100 g/min (AUC: 0.70; 95% CI: 0.75, 0.85) best described the infarct core. The acute perfusion lesion was best defined with a T_{max} of more than 6 seconds (AUC: 0.77; 95% CI: 0.73, 0.81). A double core threshold approach with a CBF of 7.5 mL/100 g/min within a lesion with a T_{max} greater than 6 seconds was more accurate for defining the acute infarct core than was the best single-threshold approach (AUC: 0.74; 95% CI: 0.70, 0.78) (Table 2). A comprehensive analysis of the results is presented in Table E3 (online).

SVD with Delay Correction

With use of SVD with delay correction, a CBF of less than 45% (AUC: 0.77; 95% CI: 0.73, 0.81) was the most accurate single threshold for defining the acute infarct core (Fig 1). A delay time of more than 2 seconds (AUC: 0.86; 95% CI: 0.84, 0.88) most accurately defined the acute perfusion lesion (Fig 2). A double core threshold approach with a CBF of less than 40% within a delay time of more than 2 seconds (AUC: 0.86; 95% CI: 0.83, 0.89) more accurately defined the acute infarct core compared with any single-threshold approach (Table 2). A comprehensive analysis of the results is presented in Table E4 (online).

Figure 1

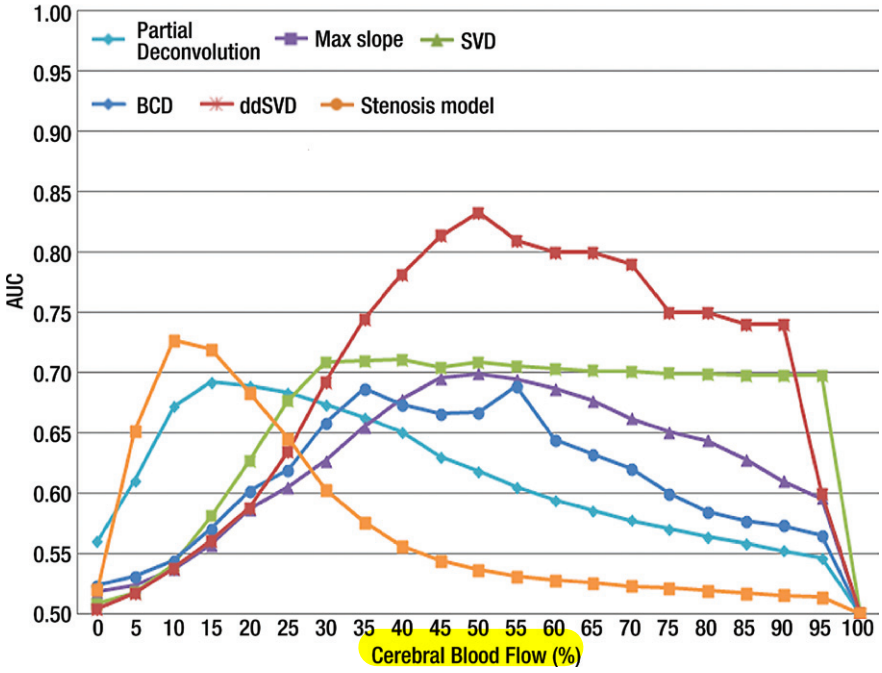

Figure 1: Graph shows AUCs of methods used to define acute infarct core with double core threshold CBF and delay time measure. Outer threshold was the optimal delay time measure threshold from Figure 2. As with perfusion lesion, delay- and dispersion-corrected SVD (*ddSVD*, red) has the largest AUC and represents the most accurate measure and threshold for determining the volume of the acute infarct core with a double threshold. *BCD* = block-circulant deconvolution.

Block-Circulant Deconvolution

With block-circulant deconvolution, an absolute CBF of less than 15 mL/100 g/min (AUC: 0.73; 95% CI: 0.7, 0.76) provided the best single-threshold definition of the acute infarct core. A relative T_{max} greater than 4 seconds (AUC: 0.72) or an absolute T_{max} greater than 5 seconds (AUC: 0.71; 95% CI: 0.66, 0.76) was the best descriptor of the acute perfusion lesion. The double threshold of a CBF less than 15 mL/100 g/min within a T_{max} greater than 5 seconds most accurately defined the acute infarct core (AUC: 0.79; 95% CI: 0.75, 0.83) (Table 2). A comprehensive analysis of the results is presented in Table E5 (online).

Stroke-Stenosis Model

With the stroke-stenosis model, an absolute CBF of less than 10 mL/100 g/min was the best threshold for defining the acute infarct core (AUC: 0.72; 95% CI: 0.69, 0.75). The acute perfusion lesion was best defined with an absolute CBF of less than 20 mL/100 g/min (AUC: 0.72; 95% CI: 0.68, 0.76). Restriction of the best infarct core threshold (absolute CBF <10 mL/100 g/min) within the acute perfusion threshold did not improve the definition of the acute infarct core (AUC: 0.72; 95% CI: 0.69, 0.75) (Table 2). A comprehensive analysis of the results is presented in Table E6 (online).

Volumetric Analysis

Results of volumetric analysis paralleled those of ROC analysis (Table 2). Thus, acute infarct core volumes derived from SVD with delay correction showed the best fit with acute diffusion-weighted MR imaging volume and results of 24-hour (major reperfusion group) analyses (r^2 = 0.72, P = .045). In addition, acute perfusion lesion volume derived from SVD with delay correction (r^2 = 0.76, P < .035) and double-threshold infarct core definition (r^2 = 0.79, P < .042) had the

Figure 2

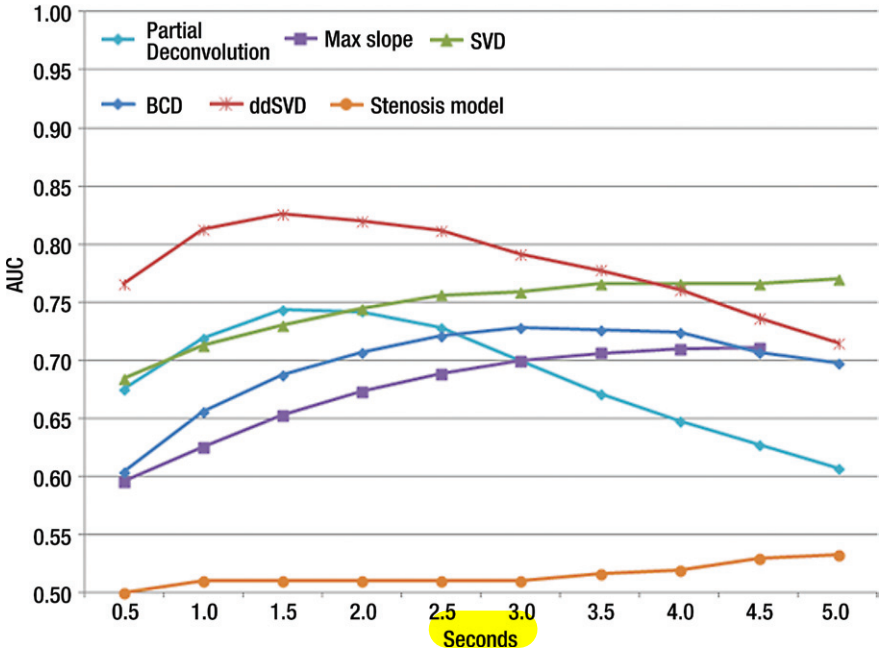

Figure 2: Graph shows AUCs of methods used to define acute perfusion lesion with delay time measures (delay time for delay- and dispersion-corrected SVD; T_{max} for SVD, block-circulant deconvolution *[BCD]*, and stenosis models; and time to peak for non-SVD methods). Delay- and dispersion-corrected SVD (*ddSVD*, red) has the largest AUC and represents the most accurate measure and threshold for determining the volume of the acute perfusion lesion. Other methods, although having a lower AUC, also show a single threshold that is optimal.

strongest relationship with lesion volume at diffusion-weighted MR imaging.

A comparison between lesion volumes at acute diffusion-weighted MR imaging and 24-hour diffusion-weighted MR imaging in patients with reperfusion showed only a small volume increase of 1.99 cm^3 (standard deviation, 1.83 cm^3; P = .43). Volumetric linear regression performed to define the acute infarct core with use of the 24-hour diffusion-weighted MR images in the 23 patients with major reperfusion who underwent acute diffusion-weighted imaging yielded very similar results (P = .62).

Discussion

In a well-characterized and large data set, we have found considerable variation in the perfusion thresholds and accuracy used to determine the core and penumbra among several commonly used perfusion algorithms. SVD with delay correction was consistently the most accurate postprocessing method, showing the best combination of sensitivity and specificity. The superiority of SVD with delay correction was confirmed in the volumetric analysis, which showed a very small difference in lesion volume between that defined at acute perfusion CT and that defined at 24-hour diffusion-weighted imaging. All postprocessing methods with the exception of the maximum slope method showed good results in the definition of the infarct core and penumbra (AUC > 0.70); however, the best threshold value varied considerably depending on the deconvolution method used. Regardless of which perfusion algorithm was used, CBF measure was the most accurate for defining the acute infarct core. This is in contrast to previously published data, which has led to CBV being a widely used core threshold to clinically define the infarct core (13). To define critically hypoperfused tissue (the outer perfusion threshold), the measures of delay (delay time, T_{max}) were the most accurate with all deconvolution algorithms (Fig 3).

An important result of the current study is the increased accuracy of the double core threshold approach for infarct core detection with all SVD methods. By restricting the infarct core threshold to within the acute perfusion lesion, the accuracy, as well as variability of the infarct core definition, was improved for all deconvolution techniques.

These findings mark a departure from the previous widely accepted view that CBV is best used to define infarct core (12). Of course, very low CBV is indicative of infarction, but no single threshold accurately defined the infarct core compared with CBF thresholds. If we increase the CBV threshold to increase the sensitivity for infarction, we then lose specificity (15,16). In addition, the commonly used threshold of a T_{max} greater than 6 seconds in stroke MR imaging to define the acute perfusion lesion is identical to that seen with our SVD (uncorrected) method for perfusion CT but is much greater than the delay time greater than 2 seconds for the acute perfusion lesion with SVD with delay correction. The different optimal thresholds seen with varying postprocessing options highlight the requirement of multicenter trials to use standardized infarct core and penumbra thresholds (9).

Understanding the theoretical underpinning of each deconvolution technique gives insights into the results. Block-circulant deconvolution is theoretically similar to SVD in the calculation of CBF, CBV, MTT, and T_{max}. However, block-circulant deconvolution is able to accurately calculate perfusion maps where the selected AIF contrast material arrival lags behind the unaffected hemisphere, typically owing to the AIF being placed in the stroke-affected hemisphere. This is achieved by block-circulant deconvolution setting a pixel-dependent partial SVD threshold to correct for potential contrast material lag. This AIF lag would otherwise cause underestimation of CBF and overestimation of MTT. However, in this study, the AIF was chosen from the contralateral to stroke hemisphere and, as a result, the accuracy of each model

Figure 3

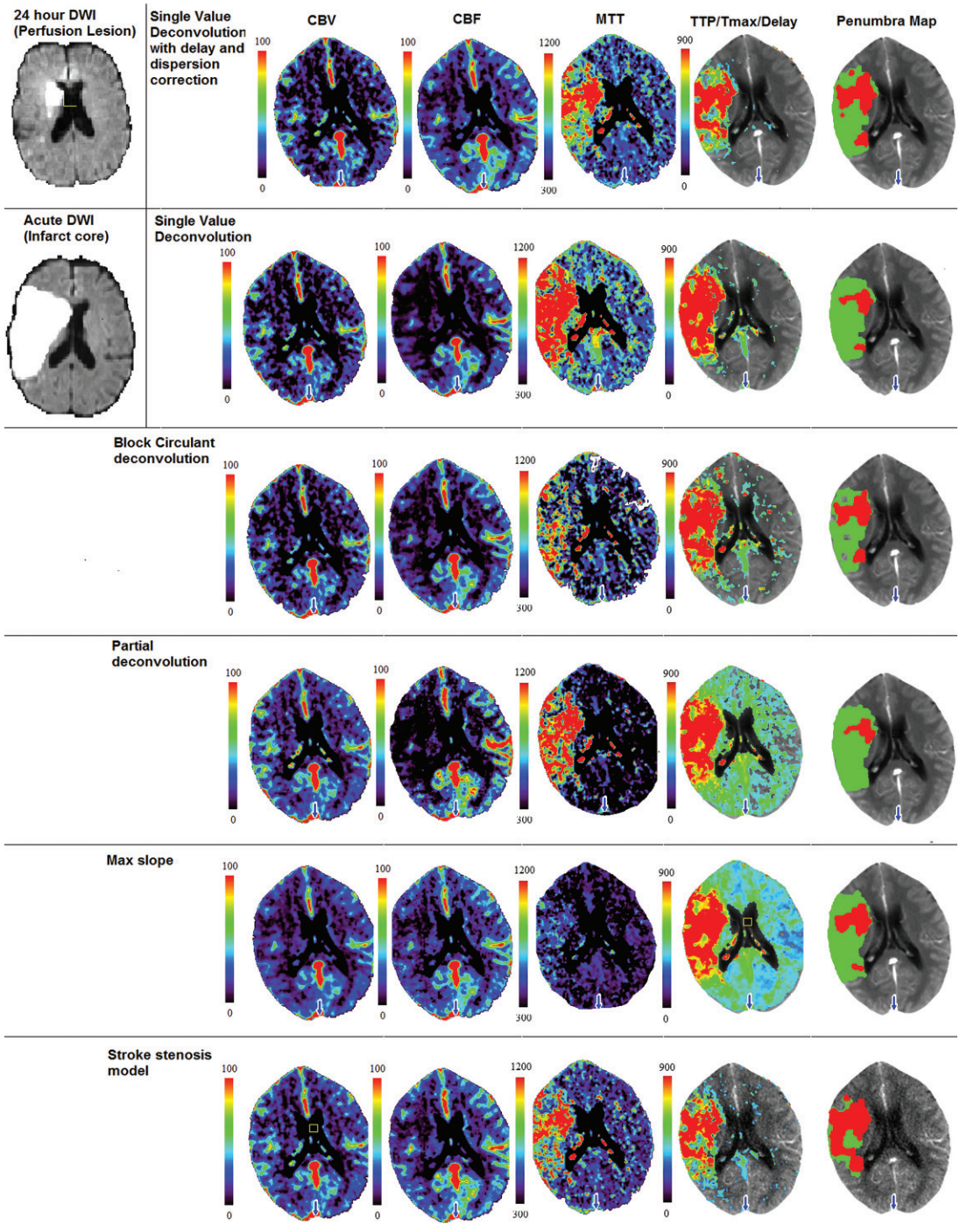

Figure 3: Comparison of output of six different methods of deconvolution in one 67-year-old man with use of same slab. Images at top left are acute and 24-hour diffusion-weighted images (*DWI*) and show the acute infarct core and total perfusion lesion after failed reperfusion therapy. Maps show CBV, CBF, MTT, and time to peak (*TTP*), T_{max}, block-circulant T_{max}, or delay time. Maps on right are core and penumbra maps, with optimal thresholds describing acute infarct core (red) and penumbra (green). There is dramatic variability in the extent of the infarct core and perfusion lesion with differing methods.

was similar, with the block-circulant deconvolution model requiring a slightly lower threshold to define tissue pathophysiology. Next, SVD with delay correction and the stroke-stenosis model each used a form of delay correction and, as such, should have similar results. However, the stroke-stenosis model uses a least-square fitting approach as its delay correction and the SVD with delay correction uses a global partial SVD cutoff (unlike block-circulant deconvolution, which uses a pixel-based partial SVD). With the stroke-stenosis model showing poor results, it is clear that the specific delay correction method used is not optimal across a large study population even though the method has the potential of being viable in individual patients.

A potential limitation of this study is the use of diffusion-weighted MR imaging as a standard of reference. However, recent studies have found that diffusion-weighted imaging is indeed an accurate measure of the infarct core when the false-positive lesion is ruled out (17) and, as such, a threshold of $b = 1000$ was applied, both acutely and subacutely. One possible limitation to this study is due to the 60-second perfusion CT acquisition time, which may cut off the input residue function of diseased pixels. This truncation effect may lead to underestimation of CBV and CBF in noncorrected models. However, from the results we see that there is only a small difference in the optimal thresholds between the postprocessing methods with dispersion correction and those without. Therefore, the effect of this truncation is likely quite limited. Another possible limitation is that the algorithms used in the current study are based on the originally published versions; CT vendors may have adjusted their postprocessing algorithms from the original versions (eg, additional noise correction or "smoothing" or different implementation of the original postprocessing method that leads to a unique model).

In conclusion, this study highlights the need for standardization of infarct core and penumbra assessment. This is important in both clinical practice and in trials in which perfusion CT is used to select "ideal" patients for acute reperfusion therapy (1). Standardized assessment of the core and penumbra is an important step in providing truly generalizable results of a multimodal CT examination. Our view is that standardized core and penumbral volume assessment is more important in enabling radiologists and neurologists to make treatment decisions than is perusal of individual perfusion CT maps, which we have shown to be highly variable across different processing platforms (18,19). This study provides an advance on current practice, where a radiologist can now apply the results of studies performed with different perfusion algorithms to their own clinical practice (1,10,11,18).

Disclosures of Conflicts of Interest: A.B. No relevant conflicts of interest to disclose. **C.L.** No relevant conflicts of interest to disclose. **N.S.** No relevant conflicts of interest to disclose. **M.P.** No relevant conflicts of interest to disclose.

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