Time-Dependent Computed Tomographic Perfusion Thresholds for Patients With Acute Ischemic Stroke

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Background and Purpose—Among patients with acute ischemic stroke, we determine computed tomographic perfusion (CTP) thresholds associated with follow-up infarction at different stroke onset-to-CTP and CTP-to-reperfusion times.

Methods—Acute ischemic stroke patients with occlusion on computed tomographic angiography were acutely imaged with CTP. Noncontrast computed tomography and magnetic resonance diffusion–weighted imaging between 24 and 48 hours were used to delineate follow-up infarction. Reperfusion was assessed on conventional angiogram or 4-hour repeat computed tomographic angiography. \( T_{\text{max}} \) cerebral blood flow, and cerebral blood volume derived from delay-insensitive CTP postprocessing were analyzed using receiver–operator characteristic curves to derive optimal thresholds for combined patient data (pooled analysis) and individual patients (patient-level analysis) based on time from stroke onset-to-CTP and CTP-to-reperfusion. One-way ANOVA and locally weighted scatterplot smoothing regression was used to test whether the derived optimal CTP thresholds were different by time.

Results—One hundred and thirty-two patients were included. \( T_{\text{max}} \) thresholds of >16.2 and >15.8 s and absolute cerebral blood flow thresholds of <8.9 and <7.4 mL/min\(^{-1}\)·100 g\(^{-1}\) were associated with infarct if reperfused <90 min from CTP with onset <180 min. The discriminative ability of cerebral blood volume was modest. No statistically significant relationship was noted between stroke onset-to-CTP time and the optimal CTP thresholds for all parameters based on discrete or continuous time analysis (\( P>0.05 \)). A statistically significant relationship existed between CTP-to-reperfusion time and the optimal thresholds for cerebral blood flow (\( P<0.001 \); \( r=0.59 \) and 0.77 for gray and white matter, respectively) and \( T_{\text{max}} \) (\( P<0.001 \); \( r≈−0.68 \) and −0.60 for gray and white matter, respectively) parameters.

Conclusions—Optimal CTP thresholds associated with follow-up infarction depend on time from imaging to reperfusion. (Stroke. 2015;46:3390-3397. DOI: 10.1161/STROKEAHA.115.009250.)

Key Words: acute ischemic stroke ■ CT ■ endovascular therapy ■ infarction ■ perfusion

Progression to infarction after acute ischemic stroke onset is time-sensitive and has substantial intersubject variability.\(^1,2\) Computed tomographic (CT) perfusion (CTP) measurement of brain parenchyma can be used to estimate ischemic core and penumbra and, therefore, provide immediate information for treatment decision-making. Current CTP thresholds that estimate these tissue states are generally derived either by comparison with magnetic resonance (MR) diffusion–weighted imaging (DWI), often done within an hour of CTP, or with follow-up infarction in patients who have reperfused sometime within 24 hours.\(^3-11\) Because infarcts grow over time and final tissue fate depends greatly on what happens in the minutes to hours immediately after this imaging snapshot, CTP thresholds predicting infarction are likely to depend on the time from stroke symptom onset to imaging, time from imaging to reperfusion, and the quality of reperfusion.

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Five recent trials have shown efficacy of endovascular treatment in patients with intracranial occlusions. Because of the recent availability of rapid and efficient endovascular treatment techniques, CTP thresholds used to predict irreversibly injured brain tissue may require revision, with attention to reperfusion quality and reperfusion time. Using a group of patients undergoing current endovascular treatment, we sought to determine CTP thresholds associated with follow-up infarction confirmed at 24 to 48 hours in patients achieving early, quality reperfusion (<90 min from CTP), in patients with reperfusion within 90 to 180 min from CTP, and in patients not achieving reperfusion acutely (ie, within 4 hours of CTP).

Methods

Patients
Data are from PrOve-IT—a prospective, multicenter cohort study with CTP imaging acute ischemic stroke patients, were included in the study if they presented within 12 hours from last seen normal. Inclusion criteria for the present study were as follows: (1) age >18 years; (2) known symptom onset time; (3) complete anterior circulation occlusion at admission or any complete posterior cerebral artery occlusion; (4) had recanalization assessed on conventional angiography at end of the endovascular treatment (modified thrombolysis in cerebral infarction [mTICI]) or on follow-up computed tomographic angiography (CTA) within 4 hours in admission imaging (patients who recanalized on follow-up CTA [modified arterial occlusive lesion score 2–3]) were excluded from this analysis because recanalization time could not be inferred from this cohort); and (5) had 24-hour follow-up imaging on MR DWI or noncontrast CT (NCCT). Demographic and clinical characteristics, medical history, physical examination, relevant workflow, and interval times were collected prospectively. The local ethics boards approved the study.

CTP Processing
An expert (Dr d'Esterre, 9 years of experience) processed each study using commercially available delay-insensitive deconvolution software (CT Perfusion 4D; General Electric Healthcare, Waukesha, WI). For each study, the arterial input function was manually selected from the basilar artery or contralateral ICA using a 2 voxel×2 voxel (in-plane) image ROI. T1-weighted and T2-weighted images over the duration of the first pass of contrast—these average maps have excellent anatomic detail and are used for gray/white matter (GM/WM) segmentation and as the source image for coregistration with follow-up imaging. In-plane patient motion was corrected in the x/y-axis using automated software (CT Perfusion 4D), and in cases with extreme motion, time points were manually removed as needed.

Image Analysis
Follow-up imaging (DWI n=77, NCCT n=55) and admission CTP average maps were coregistered using in-house software (Calgary Image Analysis and Processing Center, Calgary, AB) before being analyzed using custom software (IDL, version 6.3; RSI, Boulder, CO) using 2 different target references. For MR follow-up data, the DWI target images were resampled to match the matrix size, slice thickness, and geometry of the admission CTP average maps. (Figure 1 in the online-only Data Supplement). For CT follow-up data, the NCCT and admission CTP average maps were resampled to match the slice geometry of the admission CTA (0.625-mm slice thickness) acquisition. Both MR and CT coregistrations used the mutual information similarity metric and were performed via a multiresolution pyramid, starting with target images that have been blurred to 4 times their original pixel spacing, proceeding to images that have been blurred thrice their original spacing, and finishing with un-blurred, full-resolution images. In addition, registration parameters for the admission CTP average maps were applied to the admission CTP functional maps to register them with the follow-up MR or CT imaging data.

Two experts (Drs Ahn and Minhas) manually delineated the follow-up infarct region (ROI-1) on DWI or NCCT (when MR was unavailable) acquired between 24 to 48 hours after admission using custom software (IDL, version 6.3). Briefly, a standard window-level set-up was used to segment infarct ROIs on the coregistered follow-up MR or NCCT images. These segmentations were superimposed onto coregistered admission CTP functional maps. HU thresholds of CTP average maps were used to exclude cerebrospinal fluid and skull (<25–30 and >300 HU, respectively) manually and to separate GM from WM (35–45 HU) within the segmented infarct to arrive at ROI-1 for GM and WM separately. Regions of chronic/old infarct and evident leukoaraiosis confirmed on admission NCCT and follow-up FLAIR or NCCT (ROI-2) were removed from primary analysis.

ROI-3 was defined as any ipsilateral hemisphere brain tissue outside of ROI-1 and ROI-2. ROI-1 was mirrored onto the contralateral hemisphere at the brain midline (ROI-4), excluding chronic/old infarct and leukoaraiosis. For ROI-1 and ROI-3 individually, histograms (with 100 bins each) were created for each CTP parameter (CBF, CBV, Tmax). Two experts (Drs Ahn and Minhas) used the mTICI score at end of intra-arterial therapy to assess efficient reperfusion (mTICI 2b/3). The same experts assessed recanalization on 4-hour follow-up CTA (modified arterial occlusive lesion score 2–3 versus 0–1).

Statistical Analysis
Clinical data were summarized using standard descriptive statistics. Between group (at the CTP-to-reperfusion level stratification), differences were tested using 1-way analysis of variance or Student’s t test (as appropriate) for parametric data, Kruskal–Wallis test for nonparametric data, and the Fisher’s test for categorical outcomes (Table 1).

Patients were stratified into 2 main groups: (1) stroke symptom onset to CTP <180 min and (2) ≥180 min. Each of these 2 groups were then subdivided into 3 subgroups according to time from CTP to reperfusion, that is, (1) <90 min reperfusion, (2) 90 to 180 min reperfusion, and (3) no acute reperfusion.

Combined patient data (pooled) CTP parameter histograms of all subjects from each group were created for ROI-1 and ROI-3, respectively. These histograms were then analyzed using ROC curve and Youden’s method to determine thresholds most associated with follow-up infarction at different times of reperfusion along with respective sensitivities and specificities for each threshold. The areas under the ROC curves (c-statistics) of all parameters were compared for
significance using the Delong method. Corresponding relative CTP thresholds (for CBF) were determined by dividing the optimal thresholds by the means of the respective perfusion parameter from ROI-4.

Using individual patient-level data, CTP parameter thresholds most associated with follow-up infarction at different times of reperfusion were again derived. This was done by calculating mean±standard deviation of the ROC-derived parameters from individual patient’s histograms within a group (Table I in the online-only Data Supplement).

To test the hypothesis that optimal CTP-derived thresholds associated with follow-up infarction are dependent on time to reperfusion, we performed (1) 1-way analysis of variance across the different time strata for each optimal CTP threshold derived from patient-level data (discrete-time analysis) and (2) a locally weighted scatterplot smoothing regression to determine the association between optimal CTP thresholds derived from patient-level data and onset to CTP time and CTP to reperfusion time (continuous-time analysis).

A 2-sided P value <0.05 was considered statistically significant. All analyses were performed using R (version 3.2.1), STATA (version 13, StataCorp LP, College Station, TX), and MATLAB (R2015a, version 8.5, Mathworks Inc, Natick, MA) statistical packages.

## Results

Of a total of 146 patients satisfying study inclusion/exclusion criteria, 132 patients were included for analysis. Patients excluded had inadequate coregistration of admission and follow-up imaging studies (n=11) and CTP acquisition errors excluded had inadequate coregistration of admission and WM, respectively. CBF had the least discriminatory value among the 3 CTP parameters (Table 2).

### 90 to 180 Min CTP-to-TICI-2b/3 Reperfusion Group (n=29)

T\text{max} and CBF had similar accuracies for tissue that will infarct if reperfused late (Table 2). Optimal T\text{max} thresholds were 12.4 s (sensitivity =0.89 and specificity =0.90) and 11.2 s (sensitivity =0.81 and specificity 0.82) for GM and WM, respectively. Optimal CBF thresholds were 11.1 mL-min\textsuperscript{-1}∙100 g\textsuperscript{-1} (sensitivity =0.87 and specificity =0.93) for GM and WM, respectively.

### Nonreperfusers (n=17)

T\text{max} and CBF had similar accuracies for infarct if not acutely reperfused (Table 2). Optimal T\text{max} thresholds were 10.1 s (sensitivity =0.91 and specificity =0.87) and 9.8 s (sensitivity =0.86 and specificity =0.93) for GM and WM, respectively. Optimal CBF thresholds were 15.1 mL-min\textsuperscript{-1}∙100 g\textsuperscript{-1} (sensitivity =0.80 and specificity =0.86) and 14.9 mL-min\textsuperscript{-1}∙100 g\textsuperscript{-1} (sensitivity =0.87 and specificity =0.84) for GM and WM, respectively. Other details are in Table 2.

### Group 2: Stroke Onset to CTP ≥180 min

CT-to-TICI-2b/3 Reperfusion Group (n=14)

T\text{max} and CBF thresholds had similar accuracies for tissue that will infarct if reperfused early (Table 2). Optimal T\text{max} thresholds were 14.6 s (sensitivity =0.83 and specificity =0.85) and 14.6 s (sensitivity =0.80 and specificity =0.81) for GM and WM, respectively. Optimal CBF thresholds were 9.5 mL-min\textsuperscript{-1}∙100 g\textsuperscript{-1} (sensitivity =0.84 and specificity =0.86) and 8.3 mL-min\textsuperscript{-1}∙100 g\textsuperscript{-1} (sensitivity =0.80 and specificity =0.79) for GM and WM, respectively. CBF had the least discriminative power among the 3 CTP parameters (Table 2).
90 to 180 Min CT-to-TICI-2b/3 Reperfusion Group (n=13)

$T_{\text{max}}$ and CBF had similar accuracies for tissue that will infarct if reperfused late (Table 2). Optimal $T_{\text{max}}$ thresholds were 10.3 s (sensitivity =0.74 and specificity =0.76) and 12.2 s (sensitivity =0.69 and specificity =0.71) for GM and WM, respectively. Optimal CBF thresholds were 14.3 mL min$^{-1}$100 g$^{-1}$ (sensitivity =0.70 and specificity =0.71) and 12.6 mL min$^{-1}$100 g$^{-1}$ (sensitivity =0.79 and specificity =0.73) for GM and WM, respectively. CBV had the least discriminative power among the 3 CTP parameters (Table 2).

Nonreperfusers (n=31)

$T_{\text{max}}$ and CBF had similar accuracies for infarct if not reperfused acutely (Table 2). Optimal $T_{\text{max}}$ thresholds were 9.5 s (sensitivity =0.81 and specificity =0.82) and 10.2 s (sensitivity =0.71 and specificity =0.70) for GM and WM, respectively. Optimal CBF thresholds were 14.4 mL min$^{-1}$100 g$^{-1}$ (sensitivity =0.82 and specificity =0.80) and 15.1 mL min$^{-1}$100 g$^{-1}$ (sensitivity =0.80 and specificity =0.82) for GM and WM, respectively. Other details are in Table 2.

Optimal GM and WM $T_{\text{max}}$, CBF, and CBV thresholds associated with follow-up infarction from patient-level data analysis were similar to those from the pooled data analysis (Table 2 and Table I in the online-only Data Supplement). There was no relationship between stroke onset-to-CTP time and optimal CTP thresholds derived from patient-level data for all parameters based on discrete and continuous time analysis ($P>0.05$; Figure 1 and Figure II in the online-only Data Supplement). A statistically significant relationship was seen between CTP-to-reperfusion time and optimal thresholds for the CBF parameter ($P<0.001$ for both discrete and continuous time analysis; $r=0.59$ and 0.77 for GM and WM, respectively) and $T_{\text{max}}$ parameter ($P<0.001$ for both discrete and continuous time analysis; $r=-0.68$ and -0.60 for GM and WM, respectively; Figure 2 and Figure II in the online-only Data Supplement). The CBV parameter did not show any significant differences in optimal thresholds for any time stratification ($P>0.1$).

Discussion

We have shown that CTP thresholds associated with final infarct are primarily dependent on the CTP-to-reperfusion time. These thresholds are not dependent on stroke onset to
CTP time. In patients undergoing fast and quality reperfusion with modern endovascular treatment, we show that a CTP-derived $T_{\text{max}}$ threshold of around $>16$ s on average, in both GM and WM, has the highest sensitivity/specificity for brain tissue that is infarcted even when reperfused early (within 90 min from CTP imaging). Further, progressively lower $T_{\text{max}}$ thresholds of $>12.5$ and $>9.5$ s are associated with GM and WM infarction if reperfusion is achieved between 90 to 180 min from CTP and in the acute nonreperfusers, respectively. The CBF parameter also has a high discriminative ability in all groups, whereas CBV does not (Table 2).

With recent clinical trials showing benefit of fast and effective endovascular treatment in patients with acute ischemic stroke, this therapy will become the standard of care; however, patients with large ischemic core are unlikely to benefit from this therapy.\textsuperscript{21–24} In this context, it is important for physicians to know the extent of brain tissue that will infarct even if early reperfusion is achieved. Moreover, for physicians dealing with patients in primary stroke centers some distance away from an endovascular capable tertiary hospital, information on brain tissue that is likely to infarct in the time it takes for the patient to be transported to the tertiary center is vital.\textsuperscript{25,26} Our analysis demonstrates that optimal CTP parameter thresholds exist for identifying brain tissue that will likely infarct at different times from imaging if efficient reperfusion is not achieved (Table 2 and Figure 3; Table I in the online-only Data Supplement). These time-based CTP thresholds have the potential to help physicians in primary stroke centers make appropriate triaging decisions when directing patients for endovascular treatment to tertiary hospitals that may be 90 to 180 min away.\textsuperscript{26} These thresholds can also help neurointerventionists decide when to stop endovascular treatment if attempts at reperfusion are taking longer than expected. Figures 3 and 4 demonstrate the hypothetical time-based model and patient examples, respectively, of the utility of these time-based CTP thresholds. It is, however, possible that in patients achieving even earlier reperfusion, possibly within 60 min from imaging, that the CTP thresholds for infarct are more stringent.

In the acute nonreperfuser cohort, reperfusion status was assessed during the acute treatment process and not at 24 hours; this assessment gives us an estimate of tissue that is likely to infarct if not reperfused acutely. This threshold, along with the time-based CTP threshold we have derived for at-risk brain tissue, can give clinicians an estimate of infarct growth over time (Figures 3 and 4). We have not derived CTP parameter thresholds for penumbra (brain tissue that is likely to infarct if never reperfused). As a practical construct, this may be impossible to determine.

The absolute and relative CBF thresholds for GM and WM in early reperfusers are lower than CBF thresholds previously
reported for irreversibly infarcted brain. Factors affecting CTP processing algorithms that can lead to underestimation of CBF include delay (T0) between arterial input and ischemic tissue time density curves and use of venous curve for partial volume correction; however, the CTP algorithm used in this study is delay-insensitive, and the arterial input curve was chosen from large intracranial arteries at the base of the skull; thus, obviating the need to use a venous curve for partial volume correction. Therefore, the lower absolute and relative CBF thresholds we report are likely because of our unique data set, where many patients have undergone ultraearly and efficient reperfusion.

The use of a prolonged CTP acquisition in our study minimizes the underestimation of CBV and mean transit time from the truncation of time-density curves as compared with a shorter acquisition protocols. In spite of this, our analysis reveals that CBV is the least discriminative of the CTP parameters. Although low CBV remains strongly predictive of progression to irreversible infarction, normal CBV can be seen in both normal and severely ischemic brain tissue, and normal and elevated CBV can be seen in reperfused ischemic brain tissue.

Although we chose consecutive patients fulfilling appropriate selection criteria from a prospective study and have a small sample, given the pooling of patient imaging data for ROC analyses, our study is adequately powered to detect optimal thresholds. We also demonstrate consistency between the primary analyses (pooling of patient data) and sensitivity analyses (patient-level data). Nonetheless, validation studies need to be performed to show that these thresholds reliably predict infarction and final clinical outcome. In a minority of patients, we defined final infarct on follow-up NCCT. To address the limitation that NCCT is less sensitive than MR in detecting infarcted brain on follow-up, 2 experts (Drs Ahn and Minhas) with ≥10 years of experience delineated final infarct on NCCT by consensus.

**Figure 2.** Continuous-time analysis using patient level for optimal computed tomographic perfusion (CTP) threshold associated with follow-up infarction versus CTP-to-reperfusion time in gray matter (GM; A) and white matter (WM; B). CBF indicates cerebral blood flow; and CBV, cerebral blood volume.

**Figure 3.** Hypothetical model for time-based computed tomographic (CT) perfusion thresholds derived from the study. CBF indicates cerebral blood flow.
In conclusion, CTP thresholds associated with follow-up infarction vary based on time from imaging to quality reperfusion. These time-based CTP thresholds could potentially have important implications for clinical decision-making and triage of patients with acute ischemic stroke and proximal occlusions for endovascular treatment.

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Disclosures
Dr Goyal has a patent pending on systems of stroke diagnosis using multiphase computed tomographic angiography and a licensing agreement with GE healthcare for the same. Dr Goyal also provided consulting services to Covidien for design and conduct of SWIFT PRIME trial and for teaching engagements. Dr Hill and Dr Goyal have a research grant with Covidien to conduct clinical trials. Dr Lee receives royalties from licensing of the CT Perfusion software to GE Healthcare. The ESCAPE trial was partially funded through an unrestricted research grant by Covidien to the University of Calgary. The other authors report no conflicts.

References


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Supplemental Methods

Section I: Tmax Calculation

In the stroke protocol of CT Perfusion 4D, GE Healthcare, the impulse residue function, from which blood flow, blood volume, T0 and mean transit time maps are derived, is completely described by four parameters T0, W, E and k, where: T0 is the delay between the arrival of contrast at the artery input function and local tissue time-density curve, W is the width of initial plateau of the IRF or the minimum transit time through a tissue region, E is the fraction of the tracer that has the transit time equal to the minimum transit time. As a corollary, the remaining fraction of the tracer (1-E) would have transit times longer than the minimum transit time as described by the ‘tail’ of the impulse residue function, which is assumed to be an exponential decay function with a rate constant of k.

The Tmax value calculated by non-GE Healthcare software packages is the time of the maximum of the impulse residue function, which in our model is time at the half width of the initial plateau (W) (Figure A1). There is the additional complication that the Tmax value may or may not include the T0 value. CT Perfusion 4D calculates the Tmax as T0+0.5* AUC (of the IRF) in order to reflect both the delay in arrival and long transit time through an ischemic region. In summary, there are three ways to calculate Tmax, as shown in Figure A1

(A) Tmax=0.5*W
(B) Tmax=T0+0.5*W
(C) Tmax=T0+0.5*AUC

Method (C) used in CT Perfusion 4D (GE Healthcare) would give the longest Tmax whereas method (A) and (B) used by other non-GE Healthcare software would give the shorter Tmax values.
Figure S1. Example of co-registration between a 24-hour MR Diffusion weighted imaging (DWI) and admission CT Perfusion (CTP). CTP scans were motion corrected prior to co-registration with follow-up imaging. Shown are (A) Original MR-DWI images, (B) The co-registered MR-DWI images resampled in the same coordinate system and same slice geometry as the CTP average maps (C).
Supplemental Results

Figure SII. Box-plots (median, IQR and 95% confidence intervals) for CTP patient-level optimal thresholds derived from the discrete-time analysis for (A) gray matter and (B) white matter
Table SI. Patient-level discrete-time analysis (individual subject ROC analysis)

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<th>Onset to CTP, mins</th>
<th>CTP to reperfusion time, mins</th>
<th>Tmax (seconds)</th>
<th>CBF (ml min⁻¹ 100g⁻¹)</th>
<th>CBV (ml 100g⁻¹)</th>
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<td></td>
<td></td>
<td>GM</td>
<td>WM</td>
<td>GM</td>
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<td>&lt;90</td>
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<td>≥180</td>
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<td>Optimal Threshold (stdev)</td>
<td>15.5 (2.1)</td>
<td>15.8 (1.8)</td>
<td>7.5 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (stdev)</td>
<td>0.88 (0.08)</td>
<td>0.82 (0.08)</td>
<td>0.84 (0.04)</td>
</tr>
<tr>
<td></td>
<td>Specificity (stdev)</td>
<td>0.87 (0.05)</td>
<td>0.78 (0.10)</td>
<td>0.81 (0.05)</td>
</tr>
<tr>
<td>90-180</td>
<td>Optimal Threshold (stdev)</td>
<td>12.4 (0.93)</td>
<td>13.2 (1.6)</td>
<td>12.7 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (stdev)</td>
<td>0.89 (0.07)</td>
<td>0.82 (0.08)</td>
<td>0.84 (0.04)</td>
</tr>
<tr>
<td></td>
<td>Specificity (stdev)</td>
<td>0.87 (0.12)</td>
<td>0.75 (0.20)</td>
<td>0.85 (0.07)</td>
</tr>
<tr>
<td>Non-reperfusers</td>
<td>Optimal Threshold (stdev)</td>
<td>9.9 (1.9)</td>
<td>9.3 (1.9)</td>
<td>14.5 (4.2)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (stdev)</td>
<td>0.81 (0.11)</td>
<td>0.81 (0.08)</td>
<td>0.81 (0.12)</td>
</tr>
<tr>
<td></td>
<td>Specificity (stdev)</td>
<td>0.84 (0.12)</td>
<td>0.77 (0.15)</td>
<td>0.84 (0.07)</td>
</tr>
</tbody>
</table>

Gray matter (GM) and white matter (WM) average (stdev) patient-level optimal thresholds for Tmax, cerebral blood flow (CBF) and cerebral blood volume (CBV) for the discrete-time analysis. Also shown are the average (stdev) sensitivity and specificity for each mean threshold.