Optimal Perfusion Computed Tomographic Thresholds for Ischemic Core and Penumbra Are Not Time Dependent in the Clinically Relevant Time Window

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Background and Purpose—This study aims to determine whether perfusion computed tomographic (PCT) thresholds for delineating the ischemic core and penumbra are time dependent or time independent in patients presenting with symptoms of acute stroke.

Methods—Two hundred seventeen patients were evaluated in a retrospective, multicenter study. Patients were divided into those with either persistent occlusion or recanalization. All patients received admission PCT and follow-up imaging to determine the final ischemic core, which was then retrospectively matched to the PCT images to identify optimal thresholds for the different PCT parameters. These thresholds were assessed for significant variation over time since symptom onset.

Results—In the persistent occlusion group, optimal PCT parameters that did not significantly change with time included absolute mean transit time, relative mean transit time, relative cerebral blood flow, and relative cerebral blood volume when time was restricted to 15 hours after symptom onset. Conversely, the recanalization group showed no significant time variation for any PCT parameter at any time interval. In the persistent occlusion group, the optimal threshold to delineate the total ischemic area was the relative mean transit time at a threshold of 180%. In patients with recanalization, the optimal parameter to predict the ischemic core was relative cerebral blood volume at a threshold of 66%.

Conclusions—Time does not influence the optimal PCT thresholds to delineate the ischemic core and penumbra in the first 15 hours after symptom onset for relative mean transit time and relative cerebral blood volume, the optimal parameters to delineate ischemic core and penumbra. (Stroke. 2014;45:1355-1362.)

Key Words: computed tomography • perfusion imaging • stroke

Optimal Perfusion Computed Tomographic Thresholds for Ischemic Core and Penumbra Are Not Time Dependent in the Clinically Relevant Time Window

The critical premise of reperfusion therapies in the setting of acute stroke is to rescue the hypoxic yet potentially salvageable ischemic penumbra. Currently, the recommendations for stroke recanalization are based solely on the parameter of time, with indications for using intravenous tissue-type plasminogen activator within 3 hours of symptom onset and ≤4.5 hours in a subset of patients.1–3 For patients admitted beyond the intravenous tissue-type plasminogen activator time window, intra-arterial revascularization has been shown to have benefit in carefully selected patients.3–6 Studies using perfusion imaging have shown potential in personalizing individual patient’s treatment, independent of the time window using patient-specific image-based selection for therapy.7,8 However, the clinical relevance both of perfusion imaging and endovascular revascularization in the setting of acute stroke still remains unclear.9–11

Perfusion computed tomography (PCT) is one technique that has demonstrated potential for delineating areas of salvageable penumbra from the ischemic core.12–16 PCT is widely available in most hospital or emergency room settings, where the standard modern-day scanners are equipped with such capability. Constructing tissue fate maps to outline ischemic core and penumbra typically relies on thresholds of the PCT parameters, including absolute and relative cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT).17–20

The pathophysiology of stroke is a dynamic process influenced by multiple factors including site of vessel occlusion, amount of collateral flow, patient comorbidities, and the important factor of time.21 From this, it is logical to question whether PCT thresholds in predicting ischemic tissue fate might depend on the variable of time, which would jeopardize...
the use of this technique in making time-independent treatment decisions. A common limitation in multiple studies has been the failure to account for the potential influence of time on optimal PCT imaging thresholds. Therefore, the goal of the current study is to elucidate whether time from symptom onset to PCT imaging would alter significantly the optimal thresholds for PCT parameters used in the determination of the ischemic core and penumbra.

Material and Methods

Patients

This was a retrospective, multicenter study using data from a repository database from 3 participating institutions: the University of Virginia, Charlottesville, VA; the Center Hospitalier Universitaire Vaudois, Lausanne, Switzerland; and the University of Pittsburgh Medical Center, Pittsburgh, PA. All data were collected and analyzed in compliance with their respective institutional review boards, and any identifying information was removed as per Health Insurance Portability and Accountability Act regulations.

We looked at consecutive patients between January 2003 and June 2011 who presented with symptoms of acute stroke without hemorrhagic transformation on initial noncontrast CT image. To be included in the study, patients must have had an initial PCT imaging as part of their initial stroke work-up on presentation, had baseline and recanalization vascular imaging consisting of computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography, and had follow-up CT or MRI to assess for final infarct size. An experienced neuroradiologist with 15 years of experience manually delineated the final infarct. Only the follow-up imaging and the baseline noncontrast head CT were made available to allow determination of what was chronic infarct versus acute change. The areas of chronic infarct were not included in the estimation of final infarct. The neuroradiologist was blinded to the PCT-processed images. Clinical data recorded include the following: age, sex, and treatment received, if any. Imaging information collected include time from onset of symptoms to baseline imaging with PCT, time to recanalization imaging, and time to follow-up imaging to determine final infarct. The National Institutes of Health Stroke Scale scores were also recorded.

Perfusion CT Imaging and Processing

Both 16-slice and 64-slice CT scanners were used for the acquisition of PCT imaging. Examinations consisted of successive gantry rotations performed in cine mode during either 1 or 2 boluses of intravenous iodinated contrast material each containing 40 to 50 mL injected at 4 to 5 mL/s. Data acquisition began 7 seconds after contrast injection. The acquisition parameters were 80 kVp and 100 mAs, with a total coverage varying between 20 and 80 mm.

Images obtained by PCT were processed using the Philips Brain Perfusion software, version 4.5.2 (Philips Medical Systems, Cleveland, OH), which uses closed-form, delay-sensitive deconvolution to generate the MTT map. The arterial input was obtained from the anterior cerebral artery, whereas venous output was obtained by selecting the posterior area of the superior sagittal venous sinus. The CBV map was generated by measuring areas under the curves in each voxel and comparing them to the area under the curve in the venous output. Finally, CBF was calculated using the equation \( CBF = \frac{CBV}{MTT} \). (hours) between the onset of symptoms to baseline imaging served as a global test to determine whether there was any type of relationship between the dependent variable and the independent variable of the GAM. For each parameter, thresholds were varied independently to find the value that produced the maximal in-match with minimal out-match on initial PCT imaging. Relative thresholds were determined by normalizing the region to the normal contralateral hemisphere. Optimal thresholds for each parametric map were determined in this manner and recorded for each patient. The percentage of in-match and out-match for each parameter was also recorded. In-match was defined as the amount of voxels predicted to be ischemic by PCT expressed as the percentage of overlap with what was ultimately true infarct on follow-up. Out-match was defined as the amount of voxels predicted to be ischemic by PCT but that did not show infarction on follow-up imaging and was expressed as a percentage of the total ischemic area predicted.

In patients with recanalization (Figure II in the online-only Data Supplement), infarct on follow-up imaging was again retrospectively matched to the PCT data to identify the threshold that best predicted the ischemic core. In these patients, the final infarct was taken to represent the ischemic core at initial presentation because theoretically early recanalization should prevent further enlargement of infarction through establishing reperfusion of the penumbral tissue. For each patient and each PCT parameter, thresholds were varied independently to find the value that produced the maximal in-match with minimal out-match on initial PCT imaging. Relative thresholds were determined by normalizing the region to the normal contralateral hemisphere. Optimal thresholds for each parametric map were determined and again recorded for each patient, as well as the percentages of in-match and out-match. Both ischemic core and penumbra volume on initial PCT were recorded retrospectively using optimal thresholds.

Statistical Analysis

Data Summarization

Demographic data and other relevant clinical information were summarized by frequencies and percentages for categorical scaled variables and by the mean and the SD of the measurement distribution for continuous scaled variables.

PCT Parameter Threshold Time Trend Analyses

Time trends in the PCT parameter threshold values were examined by way of generalized additive models (GAM). For each parameter threshold, 2 separate sets of analyses were conducted. One set of analyses was conducted using the data of the patients who had persistence occlusions, and 1 set of analyses was conducted using the data of the patient with recanalization. Each set of analyses included 2 GAM analyses. One GAM examined the long-term stabilities of the PCT parameter threshold values, whereas the other GAM examined the short-term stabilities of the PCT parameter threshold values. The long-term PCT parameter threshold stability GAM analysis placing no restriction on the time between the onset of symptoms to baseline imaging, whereas multiple short-term PCT parameter threshold stability analysis restricted the time from onset of symptoms to baseline imaging to be either \( \leq 15 \), 12, or 9 hours.

For each GAM, the values of the PCT parameter threshold represented the dependent variable of the GAM model. The length of time (hours) between the onset of symptoms to baseline imaging served the independent variable of the GAM. Linear and nonlinear relationships between the dependent variable and the independent variable were examined by using a nonparametric smoothing spline function of the independent variable of the GAM. With regard to hypothesis testing, a global test was conduct to test whether there was any type of relationship between the dependent variable and the independent variable in patients with persistent arterial occlusion (Figure I in the online-only Data Supplement), infarct on follow-up imaging was retrospectively matched to the PCT data to identify the threshold that best predicted the total ischemic area. In these patients, the penumbra is expected to progress through the full extent of pathophysiological changes that ultimately result in irreversible infarct, and thus final infarction on follow-up imaging was taken to represent both ischemic core and penumbra. For each patient and each PCT parameter, thresholds were adjusted independently to find the threshold that maximally predicted the final infarct with the least amount of under- and overestimation on initial PCT imaging. Relative thresholds were determined by normalizing the region to the normal contralateral hemisphere. Optimal thresholds for each parametric map were determined in this manner and recorded for each patient. The percentage of in-match and out-match for each parameter was also recorded. In-match was defined as the amount of voxels predicted to be ischemic by PCT expressed as the percentage of overlap with what was ultimately true infarct on follow-up. Out-match was defined as the amount of voxels predicted to be ischemic by PCT but that did not show infarction on follow-up imaging and was expressed as a percentage of the total ischemic area predicted.

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variable, be it linear or nonlinear. The global test was based on the approximate F test of Hastie and Tibshirani,22 and a P ≤ 0.05 decision rule was established a priori as the null hypothesis rejection criterion for deciding whether to reject the null hypothesis that the PCT parameter threshold values were stable across time. Confidence interval construction for the predicted PCT parameter threshold time trend was based on nonparametric bootstrap percentile confidence interval methods of Efron and Tibshirani.23

Optimum Parameter Thresholds
The optimum PCT parameter threshold value was estimated by the mean of the parameter threshold empirical distribution. A nonparametric bootstrap resampling routine, with bias correction, was used to construct a 95% confidence interval for the optimum parameter threshold value. The patient-to-patient stability of the parameter threshold was quantified by the coefficient of variable. The coefficient of variation is simply the SD of the measurement distribution divided by the mean of the measurement distribution. The coefficient of variable is a unitless statistical measure of the dispersion of data points around the mean. A nonparametric bootstrap resampling routine with bias correction was used to construct a 95% confidence interval for the coefficient of variable.

Statistical Software
The software package Spotfire Splus version 8.2 (TIBCO Inc, Palo Alto, CA) was used to conduct the statistical analyses.

Results
There were 75 patients (34.6%) shown to have persistent occlusion and 142 patients (65.4%) with recanalization (Figure 1). The demographic characteristic of the two groups of patients did not differ (Table 1). The average time to recanalization imaging was somewhat greater for the persistent occlusion patients (17.5±50.9 hours; P = 0.059), than for the recanalization patients (33.6±68.0 hours). Average infarct volume on follow-up imaging also differed between the two patient groups (111.9±117.8 mL and 61.3±82.7 mL, respectively, for the persistent occlusion and the recanalization patients; P = 0.018). Average infarct volume on follow-up imaging also differed between the two patient groups (111.9±117.8 mL and 61.3±82.7 mL, respectively, for the persistent occlusion and the recanalization patients; P < 0.001).

The persistent occlusion group was first examined to determine whether the thresholds for penumbra and ischemic core varied significantly over time. In this group, there were significant changes with time in the optimal thresholds for relative CBF (P = 0.048), absolute CBF (P = 0.013), and absolute CBV (P = 0.044) but not for relative CBV (P = 0.533), relative MTT (P = 0.084), and absolute MTT (P = 0.149; Figure 2). Closer analysis by limiting the time of baseline imaging to 9, 12, and 15 hours after symptom onset showed no time-related threshold dependencies for relative CBF (P = 0.425) at any restricted time point but continued to demonstrate significant threshold variance for both absolute CBF (P = 0.012) and absolute CBV (P = 0.027; Figure 2).

Table 1. Demographic Parameters and Other Relevant Clinical Information (n=217)

<table>
<thead>
<tr>
<th>Demographic Parameters</th>
<th>Recanalized (n=142)</th>
<th>Nonrecanalized (n=75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>65.1 (14.2)</td>
<td>65.6 (14.5)</td>
<td>0.807</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>54.2</td>
<td>41.3</td>
<td>0.241</td>
</tr>
<tr>
<td>Average NIHSS at baseline (SD)</td>
<td>14.2 (5.6)*</td>
<td>14.9 (6.3)†</td>
<td>0.477</td>
</tr>
<tr>
<td>Average time from symptom onset to baseline CT perfusion imaging, h (SD)</td>
<td>6.3 (5.6)</td>
<td>5.8 (5.2)</td>
<td>0.518</td>
</tr>
<tr>
<td>Average time to recanalization imaging, h (SD)</td>
<td>17.3 (50.9)†</td>
<td>33.6 (68.0)§</td>
<td>0.059</td>
</tr>
<tr>
<td>Median time to follow-up imaging, d (IQR)</td>
<td>22.5 (7.3–60)</td>
<td>30.0 (10.8–70)</td>
<td>0.544</td>
</tr>
<tr>
<td>Site of occlusion, percentage</td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>0.7%</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery - M1</td>
<td>38.7%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery - M2</td>
<td>9.1%</td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>0.7%</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.1%</td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>Combined occlusions</td>
<td>48.6%</td>
<td>41.3%</td>
<td></td>
</tr>
<tr>
<td>No. of patients with TIMI score at baseline</td>
<td>0–118</td>
<td>0–55</td>
<td>0.112</td>
</tr>
<tr>
<td>1–24</td>
<td>1–20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–0</td>
<td>2–0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–0</td>
<td>3–0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average predicted PCT penumbra volume on initial scan, mL (SD)</td>
<td>44.3 (28.9)</td>
<td>41.9 (39.7)</td>
<td>0.611</td>
</tr>
<tr>
<td>Average predicted PCT ischemic core volume on initial scan, mL (SD)</td>
<td>34.1 (38.1)</td>
<td>48.6 (50.1)</td>
<td>0.018</td>
</tr>
<tr>
<td>Average ischemic core volume on follow-up, mL (SD)</td>
<td>61.3 (82.7)</td>
<td>111.9 (117.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PCT, perfusion computed tomography; and TIMI, thrombolysis in myocardial infarct.

*Three cases unknown.
†Twenty-nine cases unknown.
‡Nine cases unknown.
§Eight cases unknown.

Figure 1. Flowchart of the initial patient population meeting inclusion criteria for the study.
In the persistent occlusion group, the PCT parameter that best predicted the total ischemic area ought to have the highest in-match (largest overlap with the final infarct volume) and the lowest out-match (lowest percentage of area outside the total ischemic area). The in-match and out-match percentages for each PCT parameter for this group are listed in columns 5 and 6, respectively, of Table 2. Although relative MTT had the highest in-match percentage of 89.4% at a threshold of 180%, relative CBF had the lowest out-match at 9.9% at a threshold of 52%. The parameter with the second best in-match was absolute MTT at 84.5% at a threshold of 10 seconds, although the second best out-match was relative CBV at 13.3% at a threshold of 67%. The parameter with the least variability between patients as represented by the coefficient of variation was relative MTT (31.9%).

The determination of significant PCT threshold variations with respect to time was examined in the recanalization group, independent of the persistent occlusion group. In the recanalization group, we found no systematic relationship between the optimal thresholds for any PCT parameter and the duration of time between the onset of symptoms to baseline imaging (absolute CBF $P=0.312$, absolute CBV $P=0.729$, absolute MTT $P=0.772$, relative CBF $P=0.602$, relative CBV $P=0.477$, and relative MTT $P=0.770$). These data are shown in Figure 3.

In the recanalization group, the PCT parameter that best predicted the ischemic core ought to have the highest in-match (largest overlap with the final infarct volume) and the lowest out-match (lowest percentage of area outside the total ischemic area). In-match and out-match percentages for each PCT parameter are shown in columns 5 and 6, respectively, of Table 3. For the recanalization group, relative CBV at the optimal threshold of 0.66 (ie, 66%) had the both the best in-match and out-match (87.1±29.9%, 20.1±46.0%, respectively). The relative MTT had the second best in-match percentage (84.6±20.1%) at a threshold of 200%, whereas the relative CBF had the second best out-match (23.8±49.4%) at a threshold of 47.5%. Relative MTT also had the smallest coefficient of variation (27.7%; 95% confidence interval [25.6%–29.8%]), which is a relative measure of between-subject variability (Tables 2 and 3).

The volumes of ischemic core and penumbra on initial PCT were retrospectively evaluated against the time from symptom onset to baseline imaging. Overall, there was no notable trend for either infarct or penumbra size with respect to time to baseline imaging (Figure III in the online-only Data Supplement).

**Figure 2.** Optimal thresholds for perfusion computed tomographic parameters in relation to time from symptom onset in the persistent occlusion group. The graphs in the first column demonstrate the relationship of each perfusion computed tomography parameter as a function of time from symptom onset in absolute cerebral blood flow (CBF; A1), absolute cerebral blood volume (CBV; B1), absolute mean transit time (MTT; C1), relative CBF (D1), relative CBV (E1), and relative MTT (F1). Of these parameters, absolute CBF ($P=0.013$), absolute CBV ($P=0.044$), and relative CBF ($P=0.048$) significantly changed with time. The second column shows the same parameters when limited to the first 15 hours since symptom onset. Although absolute CBF and absolute CBV continued to show significant time variation, relative CBF demonstrated no significant time variation when limited to 15 hours. Predictions were made using the generalized additive model. Solid line denotes the generalized additive model marginal predictions, and hatched lines denote the lower and upper bounds of a bootstrap generated 95% simultaneous prediction interval. Overall test for trend, with respect to the nonparametric smoother function, was based on the score test of chambers.

**Figure 2 (Continued).** CBF (D1), relative CBF (E1), and relative MTT (F1). Of these parameters, absolute CBF ($P=0.013$), absolute CBV ($P=0.044$), and relative CBF ($P=0.048$) significantly changed with time. The second column shows the same parameters when limited to the first 15 hours since symptom onset. Although absolute CBF and absolute CBV continued to show significant time variation, relative CBF demonstrated no significant time variation when limited to 15 hours. Predictions were made using the generalized additive model. Solid line denotes the generalized additive model marginal predictions, and hatched lines denote the lower and upper bounds of a bootstrap generated 95% simultaneous prediction interval. Overall test for trend, with respect to the nonparametric smoother function, was based on the score test of chambers.
The primary goal of our study was to determine whether time from symptom onset to baseline PCT imaging was a significant variable in determining optimal PCT parameters and threshold to delineate the predicted ischemic core and penumbra.

Our study showed no significant variation of any PCT parameter thresholds in the first 15 hours after symptom onset for any PCT parameters in the recanalization group and for absolute MTT, relative MTT, CBF, and CBV in the persistent occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results. Beyond 15 hours, in the persistent arterial occlusion group. Limitation of time to both 9 and 12 hours had similar results.

The ideal penumbra region would include the entire tissue region that would ultimately become ischemic core if reperfusion does not occur. This volume should hypothetically be expected to not expand regardless of time dependence. However, the ischemic core is expected to grow with time if reperfusion is not established and, therefore, create increasing areas of hypoperfusion in the brain parenchyma. This leads to the hypothesis that time dependence should not alter PCT thresholds in determining penumbra, whereas core thresholds should be expected to change with time. Our data support this hypothesis when examined beyond 15 hours because only in the persistent occlusion group do thresholds eventually show significant variation, although the recanalization group has no time dependence ≤40 hours for any PCT threshold.

The secondary goal of this study was to determine the optimal thresholds for tissue ischemia. Our analysis consisted of both a persistent occlusion and recanalization group of patients. It is important to realize that this distinction is not available at the initial evaluation of patients with acute stroke in the clinical setting. In the absence of recanalization, a large penumbra invariably progress into irreversible infarct, whereas recanalization may potentially salvage the penumbra and result in improved prognosis. The prognostic value of discerning what is penumbra is, therefore, influenced by present in the late acute (beyond 15 hours) or subacute stages is not meaningful and should be avoided. In addition, these data support setting the limitation of useful PCT parameters to only those that showed no significant time variation at 15 hours, namely absolute MTT, and relative MTT, relative CBF, and relative CBV.

The P value corresponds to the overall test of trend and signifies whether there is a significant change in the optimal threshold with regard to prolonged time to baseline imaging. The coefficient of variation is the SD of the distribution of measurements divided by the mean of the distribution of measurements multiplied by 100. This quantity reflects a standardize estimate of the dispersion of the individual threshold measurements. A smaller coefficient of variation signifies less variation from patient to patient and higher reliability. In-match is the amount of infarcted tissue that was accurately predicted to be true infarct on PCT; a higher in-match implies a more accurate prediction by PCT of the final infarct size. The out-match is the area predicted by PCT to be infarct but was shown on final imaging to be noninfarcted tissue; a lower out-match signifies that the PCT did not overpredict the amount of infarct and therefore confers greater accuracy. CBF indicates cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; and PCT, perfusion computed tomography.

The optimal thresholds for these parameters demonstrated significant time variation even when time was limited to 15 h, and therefore no fixed, optimal threshold could be calculated.

### Table 2. Perfusion CT Parameters in Persistent Occlusion Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Optimal Thresholds (SD)</th>
<th>P Value Without Time Limit</th>
<th>P Value With Time &lt;15 h*</th>
<th>Coefficient of Variation, %</th>
<th>In-Match, % (SD)</th>
<th>Out-Match, % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative CBF</td>
<td>0.52†</td>
<td>0.048</td>
<td>0.425</td>
<td>44.2†</td>
<td>81.8† (23.1%)</td>
<td>8.5† (11.9%)</td>
</tr>
<tr>
<td>Relative CBV</td>
<td>0.67</td>
<td>0.533</td>
<td>0.371</td>
<td>40.4</td>
<td>66.5% (27.1%)</td>
<td>13.3% (35.6%)</td>
</tr>
<tr>
<td>Relative MTT</td>
<td>1.8</td>
<td>0.084</td>
<td>0.169</td>
<td>31.9%</td>
<td>89.4% (12.5%)</td>
<td>33.5% (81.6%)</td>
</tr>
<tr>
<td>Absolute CBF</td>
<td>†</td>
<td>0.013</td>
<td>0.012</td>
<td>56.0%</td>
<td>81.5% (21.6%)</td>
<td>14.2% (22.8%)</td>
</tr>
<tr>
<td>Absolute CBV</td>
<td>†</td>
<td>0.044</td>
<td>0.027</td>
<td>65.6%</td>
<td>72.8% (23.1%)</td>
<td>17.3% (37.0%)</td>
</tr>
<tr>
<td>Absolute MTT</td>
<td>10.0</td>
<td>0.149</td>
<td>0.097</td>
<td>45.7%</td>
<td>84.5% (19.5%)</td>
<td>16.7% (37.4%)</td>
</tr>
</tbody>
</table>

*Optimal thresholds for these parameters demonstrated significant time variation even when time was limited to 15 h, and therefore no fixed, optimal threshold could be calculated.

†Nonparametric biased corrected 95% confidence interval for the true parameter value, and therefore no fixed, optimal threshold could be calculated.

‡Nonparametric biased corrected 95% confidence interval for the true parameter value, and therefore no fixed, optimal threshold could be calculated.
whether the patient will ultimately have recanalization or not. This ranges from a best-case scenario of early recanalization and full salvage of penumbra tissue to the worst-case scenario of no recanalization and final infarct growth to include the entire penumbra.\textsuperscript{27} The importance of this consideration has been stressed in literature.\textsuperscript{28,29} Therefore, the rationale for separating patients based on recanalization status in our study is that it allows for the assessment of optimal PCT thresholds for both the best-case (ischemic core) and worst-case (total ischemic area) scenarios.

In the persistent occlusion group, the optimal threshold to delineate the total ischemic area was relative MTT at a threshold of 180%. This finding is consistent with multiple studies in literature and represents an ideal parameter because of similar values in both gray and white matter, which may otherwise be a confounding variable.\textsuperscript{17,19,30,31} Although relative MTT was the optimal parameter overall (balancing in-match, out-match, variance, and time independence), relative CBF with a threshold of 52% showed significantly less overestimation than relative MTT. Other studies in literature have supported relative CBF as the optimal threshold, either as an independent parameter or in combination with relative MTT.\textsuperscript{20,31} Similarly, our study shows that both these parameters provide accurate measures of the total ischemic area.

In patients with recanalization, the optimal parameter to predict the final infarct was relative CBV at a threshold of 66%. Relative CBV also had the least overestimation of infarct, although no parameter completed avoided the generation of false-positives. Our results are in contrast to the study by Wintermark et al,\textsuperscript{17} who found that the optimal parameter in patients with early recanalization was absolute CBV but consistent with other studies in the literature, including one that found a relative CBV threshold of 56% to be optimal.\textsuperscript{32} Interpretation for this group is more challenging given that immediately successful recanalization theoretically stops infarct evolution, but recanalization occurring after the baseline PCT imaging would allow the infarct to grow over the penumbra before this process is stopped and the remaining penumbra salvaged.

Although, on average, the penumbra in absence of recanalization will transform progressively into irreversible infarction, it is not possible to determine the ratio of penumbra and ischemic core for each patient based simply on time. Specific time frames have been described for therapy guidelines, but although evolution of acute stroke is indeed time dependent, it is also incredibly patient specific. This is supported in the present study, where patients presenting even ≤24.5 hours were shown on PCT to have varying areas of penumbra and no trend with regard to the ratio of penumbra to ischemic core with respect to time from symptom onset (Figure III in the online-only Data Supplement). Although the ischemic core

Figure 3. Optimal perfusion computed tomographic parameters in relation to time from symptom onset in the recanalization group. The first column shows parameters when no limitation is applied for absolute cerebral blood flow (CBF; A1), absolute cerebral blood volume (CBV; B1), absolute mean transit time (MTT; C1), relative CBF (D1), relative CBV (E1), and relative MTT (F1). The second column shows the same parameters, absolute

Figure 3 (Continued). CBF (A2), absolute CBV (B2), absolute MTT (C2), relative CBF (D2), relative CBV (E1), and relative MTT (F2), when time is limited to the first 15 hours from symptom onset. Predictions made using the generalized additive model. Solid line denotes the generalized additive model marginal predictions, and hatched lines denote the lower and upper bounds of a bootstrap generated 95% simultaneous prediction interval.
will grow with increasing time, the rate at which this transformation occurs is patient specific and is influenced by multiple variables, such as the richness of the collateral circulation. The inability to determine ischemic core and penumbra adequately based on time alone supports the necessity for technologies that are specific to the determination of the optimal thresholds. A smaller coefficient of variation signifies less variation from patient to patient and higher reliability. In-match is the amount of infarcted tissue that was accurately predicted to be true infarct on PCT; a higher in-match implies a more accurate prediction by PCT of the final infarct size. The out-match is the area predicted by PCT to be infarct but was shown on final imaging to be noninfarcted tissue; a lower out-match signifies that the PCT did not overpredict the amount of infarct and therefore confers greater accuracy. CT indicates computed tomography; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; and PCT, perfusion computed tomography.

Conclusions

In summary, our study of 217 patients shows that optimal PCT parameters to delineate ischemic core (relative CBV) and penumbra (relative MTT) do not significantly vary with time in a clinically relevant window of \( \leq 15 \) hours since symptom onset. Beyond 15 hours, time is a significant factor and PCT results should not be interpreted using the same thresholds as in the acute phase.
Disclosures

Dr Jovin has a stock/other ownership interest to disclose with Silk Road Inc. Dr Michel has a research grant to disclose with Swilli Cardiology Foundation and Cardiomet Centre Hospitalier Universitaire Vaudois, speaking engagements to disclose with Boehringer Ingelheim, Covidiem, and Pfizer, and consultant/advisory board to disclose with Pierre Fabre, Bayer, and Pfizer. The other authors report no conflicts.

References

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