Rapid Perfusion Abnormality Estimation in Acute Stroke With Temporal Correlation Analysis

Yueh Z. Lee, MS; Jin-Moo Lee, MD, PhD; Katie Vo, MD; Chung Y. Hsu, MD, PhD; Weili Lin, PhD

Background and Purpose—Determination of the presence or absence of ischemic penumbra through diffusion-perfusion mismatch requires rapid delineation of both abnormalities. Although singular value decomposition–based perfusion parameter estimation has offered valuable insights into the underlying cerebral hemodynamics, the associated postprocessing procedures have limited its widespread use. We explored the utility of a simple technique to define perfusion abnormality in acute stroke patients.

Methods—Twenty acute stroke patients were studied. The MR dynamic contrast approach was used to obtain cerebral blood flow, cerebral blood volume, and mean transit time (MTT). Temporal correlation was used to correlate 4 reference functions—an arterial input function (AIF), a normal tissue function, a lesion function, and a venous output function—with dynamic contrast MR images, and correlation coefficients (CCs) were calculated pixel by pixel. In addition, chronic-state T2-weighted images were coregistered onto the images acquired acutely for assessing the sensitivity and specificity of CC-defined lesion.

Results—Statistically significant differences in cerebral blood flow and MTT were found between CC-defined normal and abnormal tissues with all 4 reference functions used. When the final infarct volume was used as the gold standard, a similar sensitivity between MTT (78%) and AIF (76%) CC-defined lesion was obtained, whereas the specificity was higher for AIF (61%) than that obtained with MTT-defined lesion (52%).

Conclusions—We explored CC maps as a simpler alternative of estimating perfusion abnormality, and results demonstrated the potential clinical utility of a correlation-based technique for estimating brain perfusion status. (Stroke. 2003;34:1686-1692.)

Key Words: hemodynamics ■ magnetic resonance imaging

It has been suggested that in acute stroke the mismatch between diffusion- and perfusion-defined abnormal regions may represent potentially viable tissue at high risk for infarction if blood flow is not rapidly restored.1–5 With this concept in mind, many investigators have used these imaging approaches to determine the presence of diffusion-weighted imaging–perfusion-weighted imaging (DWI-PWI) mismatched regions in an attempt to identify reversibly injured brain tissue and individualize therapeutic time windows for patients.3,6–9 The ability to rapidly define the DWI-PWI mismatch is thus of potentially great importance from both clinical and research perspectives.

The MR acquisition methods associated with both techniques are rapid and easily acquired within a clinically relevant timeframe. Postprocessing for DWI is fast and available immediately for clinical interpretation. The identification of perfusion abnormalities is not as readily accessible. Although quantitative estimates of cerebral hemodynamics, including cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT), have been demonstrated,10 determining abnormalities on CBF and CBV maps can be challenging because of the physiological differences between gray and white matter. In contrast, the differences on MTT maps are minimal, making it more straightforward to depict regions with perfusion deficiency. To date, therefore, most studies have relied on MTT maps for the determination of perfusion defects. The calculation of MTT maps is complex and requires the selection of an arterial input function (AIF), likely to induce substantial variability.11,12 Semiautomated or automated techniques have been proposed but are not widely used.13

Temporal correlation (TC) has been widely employed for functional MRI studies.14 With a predefined reference function, correlation coefficients (CCs) can be calculated pixel by pixel to determine the similarity between the reference and the temporal signal changes during functional MRI experiments, potentially revealing regions of activation. The analogous TC approach can be used to determine the extent to which cerebral hemodynamics is altered during cerebral ischemia. With a dynamic imaging approach, temporal signal
changes reflecting the passage of the contrast agent can be correlated with a predefined reference function. When the arrival time of the contrast agent and the shape of the contrast-induced signal changes are identical to that of the predefined reference function, a CC of 1 will be obtained. A CC < 1 will be obtained when discrepancies between the experimentally obtained temporal signal and the reference functions exist. In this study, we explored the use of TC analysis as a rapid method of defining brain perfusion status in acute stroke patients. The sensitivity and specificity of CC- and MTT-defined lesions with respect to the chronic lesions were also investigated.

Methods
Patients were recruited as a part of clinical trials with the following inclusion criteria: age > 18 years, first acute ischemic stroke, and the ability to perform MRI within 8 hours of stroke onset. Patients were excluded for the following reasons: prior or bilateral strokes, baseline CT scan with evidence of hemorrhage, and contraindication for MRI. This study was approved by the Institutional Review Board. Twenty patients were studied after obtaining informed consent. Each patient was scanned with a protocol that included DWI, T1, T2, and PWI. PWI consisted of a gradient-echo echo-planar imaging sequence repeated 40 times. A 0.1-mmol/kg dose of Gd-DTPA was injected after the end of the fifth scan. CBF, CBV, and MTT were calculated from the techniques described by Østergaard et al.15 with the correction scheme for absolute CBF described by Lin et al.10 A more detailed description can be found elsewhere.10 An AIF from the contralateral middle cerebral artery was selected to serve as the reference function for the singular value decomposition (SVD). The area underneath a venous output function (VOF) selected from the sagittal sinuses provided a normalization factor for the CBF calculation.10

Patients were subsequently imaged at either 1 week (n = 8) or 12 weeks (n = 7) after stroke onset to obtain the final infarct on T2-weighted images. The selection of the chronic imaging time was limited to the constraints of the clinical trial protocols. The T2-weighted images from 5 patients were not available because of lack of follow-up.

The normalized CC was calculated for each pixel as follows:

\[
CC = \frac{\sum_{i=1}^{N} S(t_i) \sum_{i=1}^{N} R(t_i)}{\sum_{i=1}^{N} S(t_i)^2 \sum_{i=1}^{N} R(t_i)^2}
\]

where \( S(t_i) \) and \( R(t_i) \) represent the signal of a pixel of the time series images and reference function, respectively, and \( N \) indicates the total number of time points.

In this study, 4 reference functions were used, including the AIF, VOF, tissue function (TF), and lesion function (LF). The AIF and VOF CC maps were created with the AIF and VOF selected for the creation of the hemodynamic maps. TF and LF were selected by drawing regions of interest (ROI) contralateral to and within the lesion, respectively. Both ROIs were based on the DWI images and were \( \sim 100 \) pixels in size.

Transit time (TT) and time to peak (TTP) maps were calculated as follows. Contrast arrival time was determined as the first time point that was greater than the time of maximum concentration, and its concentration was less than the mean ± 2 SD of the 5 final points in the concentration curve. The time difference between the arrival time and time-point return to baseline was defined as the TT.

Defining the CC Lesion Threshold
To determine whether 2 distinct distributions, representing the putative normally and abnormally perfused tissues, were present in the CC maps, a large ROI was drawn encompassing a slightly larger size of normal compared with suspected lesion areas based on MTT maps. A histogram was then created with a bin width of 5 gray levels and a 3-point moving average filter. Normally, only 2 peaks were seen in the histograms, representing normal and abnormal perfusion. First, the highest peak of CC values was found as the histogram bin with the highest number of counts. Then, the next-highest peak for the CC distribution was found by searching for the maximum counts in the range 20% away from the first peak. The 20% exclusion range was arbitrarily selected to facilitate the search; it proved sufficient and reasonable for all patients. The CC threshold was defined as the histogram bin with the minimum number of counts between the 2 peaks.

The CC threshold was subsequently used to determine brain regions for the measurements of CBV, CBF, MTT, TT, and TTP. Pixels with a value less than the CC threshold were defined as abnormal when AIF and TF were used as the reference functions. In contrast, pixel values exceeding the CC threshold values were considered abnormal tissues when LF and VOF were used. Mean and SD of the perfusion parameters for abnormal regions were calculated for each of the 4 reference functions. A similar ROI in the contralateral hemisphere was used to obtain normal values.

Lesion Volume Comparison
To determine the sensitivity and specificity of CC-defined lesions, the chronic T2-weighted images were coregistered to the acute T2-weighted images (b = 0 of the DWI) using Automated Image Registration.16 The acute DWI images were acquired in registration with the PWI images; thus, the chronic T2-weighted images were registered to the acute perfusion maps. The final infarct, measured by manually outlining regions with hyperintensity on the coregistered T2-weighted images, was used as the gold standard. MTT-defined lesion volume was determined as pixels within the abnormal hemisphere having MTT values greater than mean ± 2 SD of that obtained from the contralateral hemisphere. The same approach mentioned previously for determining CC-defined abnormal areas was used to determine the lesion volume in the CC maps. Only lesion volumes as defined by the AIF and TF were selected for analysis of sensitivity and specificity for revealing the final lesion volume because they were the reference functions that were able to separate lesion from nonlesion in all patients. Finally, lesion volumes determined by the CC AIF, CC TF, and MTT maps were compared with those determined by the chronic T2-weighted images.

Statistical Analysis
Two-tailed unpaired \( t \) tests were performed between each set of perfusion parameters to determine whether the 2 regions separated by the CC threshold had statistically different hemodynamic parameters. Tukey’s test between volumes of abnormal perfusion as defined by MTT, AIF CC, and TF CC compared with the chronic T2-weighted images was also performed. Sensitivity and specificity of CC- and MTT-defined lesions were calculated with respect to the final lesion obtained from the coregistered chronic T2-weighted images.

Results
A summary of the patient information is given in Table 1. Of the 20 patients, 6 received intravenous thrombolytic therapy; however, no recanalization was observed for any of the 6 patients during the MRI session in the acute phase. Repre-
sentative CC maps and the corresponding PWI images are shown in Figure 1 from 1 patient (patient 12, Table 1). Perfusion deficit is evident in CBF (Figure 1a), MTT (Figure 1b), TTP (Figure 1c), and TT (Figure 1d) maps in the right middle cerebral artery territory. The CC maps, generated with 4 different reference functions—AIF (Figure 1e), TF (Figure 1f), LF (Figure 1g), and VOF (Figure 1h)—demonstrated similar areas of decreased perfusion; lesions generally appeared darker relative to areas of normal tissue, representing reduced correlation coefficients. Reverse contrast was seen, however, when LF and VOF were used as the reference functions. CC maps from the AIF or TF demonstrated lesions that were more visually apparent compared with those generated with LF or VOF. The chronic T2-weighted image at the same location is also shown in Figure 1i.

The corresponding reference functions of Figure 1 are shown in Figure 2 (top row). The AIF always demonstrates the earliest arrival time, and the LF exhibits delayed flow compared with the TF. The histograms of correlation coefficients obtained from the predefined ROI for each of the reference functions are also shown in Figure 2 (middle and bottom rows). It is evident that all the histograms have 2 well-separated peaks.

Results obtained from another patient are shown in Figure 3 (patient 2, Table 1). Similar to Figure 1, perfusion deficit is evident in CBF (Figure 3a), MTT (Figure 3b), TTP (Figure 3c), and TT (Figure 3d) maps in the right middle cerebral artery territory. The CC maps also demonstrate the perfusion deficits (Figures 3e through 3h), although the lesion is most pronounced in the CC map derived from the AIF (Figure 3e). Histogram analysis of the data from this patient reveals a single distribution when VOF and LF were used as reference functions (Figure 4, bottom row), making it difficult to determine an appropriate CC value for separating normal and abnormal tissues.

CC threshold values were not attainable in 2 and 5 patients when LF and VOF, respectively, were used as reference functions. These patients were excluded from data analysis for obtaining the following results. The average threshold values demarcating the CC-defined lesion from nonlesion for AIF, TF, LF, and VOF were 0.47 ± 0.15, 0.64 ± 0.12, 0.30 ± 0.26, and 0.51 ± 0.14, respectively.

The mean perfusion parameters obtained from CC-defined normal and abnormal areas are summarized in Table 2.

### Table 1. Patient Demographic Data

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**Mean ± SD** 70 ± 9.6, 14.6 ± 5.7, 4.3 ± 1.3

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Figure 1. Hemodynamic parameter maps for patient 12 (Table 1): CBF (a), MTT (b), TTP (c), TT (d), AIF CC (e), TF CC (f), LF CC (g), VOF CC (h), and chronic T2-weighted map (i). Note the areas of decreased correlation on the AIF and TF CC maps and areas of increased correlation on the LF and VOF CC maps, both representing perfusion abnormality.
Except for CBV, measurements of CBF, MTT, TT, and TTP were significantly different between the CC-defined areas of perfusion abnormality and normal tissues, suggesting that the CC techniques were indeed capable of separating areas of perfusion abnormality from normal tissues.

The AIF CC-defined lesion volumes were on average 10 \frac{\%}{21} smaller than MTT-defined volumes (P < 0.05), whereas the TF CC-defined lesion volumes were on average 27 \frac{\%}{22} smaller than the corresponding MTT-defined volumes (P < 0.001). However, the AIF CC and TF CC lesion volumes were not significantly different from each other.

Chronic T2-weighted images were available from only 15 of the 20 patients in the study because of death (n = 1) or lack of follow-up (n = 4). In the patients for whom the final infarct volumes were available, the MTT-defined lesion had the highest sensitivity (78\%), followed by AIF CC-defined (76\%) and TF CC-defined (65\%) lesions, compared with that obtained from the final infarct defined by T2-weighted images. In contrast, the specificity for MTT-defined lesions was the lowest (52\%), followed by AIF CC-defined (61\%) and TF CC-defined (68\%) lesions.

**Discussion**

Although the concept of correlation is widely used in statistical analysis, its uses for the estimation of perfusion related parameters have been limited.\textsuperscript{17-19} Lo et al\textsuperscript{19} used CT and TC to estimate the time lag between a contralateral reference function and the pixel of interest, essentially an estimate of TT delay. This technique suffers from limitations similar to those of TT or TTP maps, discussed below. In addition, these studies were performed only in ischemic animal models, and systematic comparison with the currently available perfusion parameters was not performed.\textsuperscript{20,21}

Four reference functions—the input (AIF) and output (VOF) blood flow to the brain and the perfusion behavior in normal (TF) and abnormal (LF) tissue—were evaluated. These reference functions represent the main physiological blood flow patterns present in the brain and were chosen to compare their ability to delineate perfusion deficits. Through histogram analysis, 2 separate peaks (Figure 2) were consistently observed when either AIF or TF was used as the reference function, representing similar and dissimilar...
concentration-time curves compared with the reference function used. However, some patients had histogram distributions that were not separable into 2 distinct peaks when either VOF (n=5) or LF (n=2) was used. This lack of separation is likely caused by the heterogeneous nature of the blood flow to the lesions. For example, in Figure 4 (top row), the TF and LF have similar arrival times (LF is just slightly delayed), making it difficult to separate the normally perfused tissue from the lesion through the use of LF (Figure 4, left panel, bottom row). The complexity in separating the different areas of flow may also be reflected by 3 possible flow patterns within the hemisphere with abnormally perfused tissue. When the LF or VOF is considered the reference function, 2 distributions of abnormal flow can be observed: 1 centered about zero correlation and 1 at a high correlation. The pixels with values centering about zero correlation represent tissue having no signal change (ie, receiving no blood flow). In regions with some perfusion, albeit at a low and abnormal level, the correlation will be expected to be high. The pixels with normal perfusion, however, will exhibit lower correlation (but positive) values compared with the poorly perfused tissue. Thus, the distribution of normal tissue on the histogram is likely surrounded by the 2 distributions of abnormal tissue, rendering it difficult to separate out the normal from abnormal perfusion.

Cerebral Hemodynamics in CC-Defined Abnormalities

Although 2 distinct distributions are normally observed in the histogram analysis, particularly with AIF and TF as reference functions, their relationships with the underlying cerebral hemodynamics need to be addressed. It is evident from Table 2 that the CC-defined lesions demonstrate statistically lower CBF and higher MTT, TT, and TTP compared with the CC-defined normal tissue, regardless of the reference functions used, suggesting that CC can be used to differentiate areas of perfusion deficit. No significant differences are observed for the measured CBV between CC-defined normal and abnormal tissues, which may reflect the complex pattern of compensatory CBV changes during acute stroke. The hemodynamic parameters were calculated on the basis of a contralateral AIF, which may potentially introduce systematic errors in the calculation of CBF or MTT. However, from the results of Lythgoe et al and our own experiences with AIF selection, we felt that this selection was appropriate for the present study and would not change our conclusions.

Comparisons of Lesion Volumes

Several different approaches have been proposed for identifying regions of brain tissues with perfusion deficient, including MTT, TT, and TTP maps. Unlike MTT maps, TT and TTP can be automatically calculated and are available for clinical interpretation immediately after imaging. However, estimations of these 2 parameters are inherently limited by the temporal resolution (effective repetition time [TR]) of the PWI sequence. For example, a TR of 2.0 seconds was used in this study. Given that the average TTP for abnormal and normal tissues was 6.25 ± 1.77 and 3.64 ± 1.28 seconds, respectively, similar to the published results, the number of time points separating areas of abnormal perfusion is zero, making it difficult to distinguish areas of perfusion deficit. Similar limitations are also associated with TT. In contrast, MTT maps are preferred for identifying deficits because there is a better demarcation between lesion and nonlesion. However, the additional complexity associated with the SVD required for estimating MTT has prolonged its post-processing and has limited its use in the acute stroke setting.

One of the ultimate goals for performing PWI is to predict the final lesion volume for patients. As shown in Figures 1 and 3, the AIF- and TF-defined lesion volumes were significantly smaller than that defined by MTT. This is interesting because many investigators have pointed out that MTT often overestimates the true extent of final lesion volumes. The overestimation is also demonstrated by our data because MTT has the lowest specific...
ity in predicting the final lesion volume. In contrast, relative to the MTT, the AIF CC demonstrates similar sensitivity to the detection of the final lesion volume but with higher specificity. The difference may reflect the extra sensitivity of the CC technique to the shape of the bolus curve, beyond the timing differences to which both the CC and MTT are sensitive. Further validation of the TC technique against more widely accepted perfusion standards such as nuclear medicine–based techniques will be useful to obtain a better understanding of the clinical value of TC.

The increased specificity and reduced sensitivity of the TF CC over the AIF CC may reflect differences in timing. The later-arriving TF may have components that overlap the LF. Thus, using the AIF as the reference function would probably provide improved detection of perfusion deficit. Even without the selection of an AIF as required by the deconvolution techniques, the CC technique is still capable of discerning perfusion abnormalities. Thus, the CC-based technique is less dependent on an accurate and exact selection of an AIF, unlike the SVD-based methods.

Study Limitations
In general, the dynamic susceptibility contrast technique suffers from TR limitations, even beyond the poor TTP and TT resolution mentioned previously. This limited time resolution results in an imperfect AIF selection, which may lead to errors in the estimation of hemodynamic parameters, including CBF, CBV, and even the CC. Shortening the TR to improve time resolution, however, results in reduced signal-to-noise ratio and poor-quality images. A TR of 2 seconds was used in our studies as a compromise for the image quality and the accuracy of CBF, CBV, and CC estimates. More studies are required to further evaluate the potential errors induced by TR choice.

The patients in this study were recruited as a part of clinical trials with fixed imaging protocols. Eight of the patients were imaged at 1 week after symptom onset, potentially allowing the stroke lesion to evolve further. Therefore, the estimation of lesion volume may not represent the true final lesion volume for these 8 patients and may potentially confound the calculation of sensitivity and specificity.
Finally, the CC technique appears to be a robust method for rapidly visualizing tissue with abnormal perfusion in acute stroke. Lesion delineation is also demonstrated to be straightforward using a derived threshold. Although it lacks a corresponding physiological parameter, TC may be a useful addition in the imaging of stroke and other pathologies.

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References
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