Fragmentation of the Classical Magnetic Resonance Mismatch “Penumbral” Pattern With Time

Henry Ma, MBBS, FRACP; Jorge A. Zavala, MD; Hock Teoh, MRCP; Leonid Churilov, PhD, BSc; Marveyles Gunawan, BComp; John Ly, MBBS, FRACP; Peter Wright, FRACP; Thanh Phan, PhD, FRACP; Shuji Arakawa, MD, PhD; Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP

Background and Purpose—The classical mismatch pattern in the middle cerebral artery territory stroke on MR is defined by a central diffusion-weighted image core with surrounding mismatch tissue. Because of variable rates of tissue salvage, we hypothesized that this pattern may fragment over time and may be influenced by vessel patency, mismatch volume, and infarct core location.

Methods—Patients were recruited with MR studies performed within 48 hours of ischemic stroke. Mismatch patterns based on diffusion-weighted/perfusion-weighted images were categorized as classical (majority of the diffusion-weighted image within the perfusion-weighted image lesion) or nonclassical (fragmented) patterns. The proportion of patterns was assessed with reference to time, vessel patency, mismatch volume, and infarct core location.

Results—Sixty-seven patients (33 classical [49.3%] and 34 nonclassical patterns [50.7%]) were studied within 48 hours (median age, 74.0 years). Compared to the nonclassical pattern, the classical pattern had a shorter time to MR (3.4 hours vs 10.4 hours; \(P=0.004\)) and a larger mismatch volume (62.0 mL vs 3.5 mL; \(P<0.0001\)). The positive predictors for the classical pattern were earlier time, vessel occlusion, superficial core location, and larger mismatch volume.

Conclusion—The classical mismatch pattern may fragment with time. Over 48 hours the classical pattern is seen earlier after stroke onset, with higher rates of vessel occlusion and larger mismatch volumes. (Stroke. 2009;40:3752-3757.)

Key Words: diffusion-weighted imaging ■ ischemia ■ magnetic resonance ■ ischemic stroke ■ penumbra

With the advances of neuroimaging there has been significant improvement in the imaging of the anatomic and functional status of the cerebral tissue in experimental and clinical studies of ischemic stroke. Using MRI, diffusion-weighted images (DWI) have provided a reasonable representation of the infarct core and the mismatch between DWI and perfusion-weighted images (PWI) is considered to approximate the ischemic penumbra.1–3

The ischemic penumbra was typically represented by a more or less centrally located infarct core that was surrounded by a rim of penumbral tissue. Beyond this was a zone of hypoperfused tissue with normal cellular and electrophysiological function or “benign oligemia.”2,4,5 This concept formed the basis of calculations of penumbral volumes in most studies using MR. In other words, it was assumed that growth of the infarct core (DWI) would always occur into the hypoperfused tissue (PWI) in a uniform fashion if reperfusion did not take place in a timely fashion. However, various factors can affect the salvage of the ischemic penumbra, such as collateral circulation, recanalization, and reperfusion at differing times, as well as variability in ischemic thresholds between white and gray matter.2,6,7 These factors may result in a nonuniform penumbral salvage, which may only become obvious when precise coregistration of PWI and DWI is performed. Because the majority of MR DWI/PWI studies of mismatch volumes have been performed within the first 6 hours after stroke onset, these issues may not have been particularly important if the classical mismatch pattern is maintained during this period. However, given that any variability in mismatch salvage is more likely to become greater with time and that therapeutic time windows for intervention are being constantly extended, a better understanding of this issue is important.

To investigate this further, we hypothesized that there may be a fragmentation of the classical DWI/PWI mismatch pattern with time after stroke onset. This may be influenced by vessel recanalization infarct volume and location.

Patients and Methods

Patients

Patients older than age 18 years who presented with acute hemispheric ischemic stroke within 48 hours of stroke onset without contraindication to MR were recruited subject to MR availability. Inclusion criteria included the presence of DWI and a clinically relevant PWI defect in the
contralateral MCA. Smoothing was performed using a smear filter and a time direction smoothing using a (1-2-1) mask to reduce noisy data.

The chosen arterial input function was the normal saline. The Magnetom Avanto Syngo MR2004V has values 0.2 mmol/kg was injected by a power injector, followed by 15 mL normal saline. The Magnetom Avanto Synco MR2004V has values for T2 of TR/TE 3500/100 ms and for DWI of TR/TE 1200/100 ms. Time of flight magnetic resonance angiogram was performed, which included the intracranial portion of the internal carotid artery, the circle of Willis, and the proximal MCA.

### Image Analysis

#### Core Lesion

All voxels with DWI image intensity reading 1.4 times or more compared to the mean DWI image intensity value of the contralateral (normal) cortical hemisphere were included using the Analyze software (Biomedical Imaging Resources, Mayo Clinic).\(^9,10\) The artifact voxels were removed manually after visual assessment.

#### Perfusion Map

Raw perfusion images were processed by StrokeTool (Digital Image Solution, H. J. Wittsack). The chosen arterial input function was the contralateral MCA. Smoothing was performed using a smear 3×3 filter and a time direction smoothing using a (1-2-1) mask to reduce noisy data.

Tmax perfusion maps were calculated according to the singular deconvolution method. Tmax is the time delay to the maximal residual function. The concentration time course of each voxel is deconvolved with the arterial input function using singular value decomposition algorithm.\(^9,10\) All the voxels of the affected hemisphere that equaled and exceeded the mean Tmax value of the contralateral (normal) hemisphere were included as part of the Tmax 2 seconds plus perfusion map using Analyze software (Biomedical Imaging Resources, Mayo Clinic). The lesions were delineated after the coregistration process. Artifactual voxels such as those within the ventricular spaces and the leptomeningeal region were identified and excluded after coregistration of the PWI and DWI images.

#### Coregistration of Images

The final T2-weighted image was chosen as the target common space. If the final T2 image was not available, then the acute DWI image was used as an alternative. Careful manual coregistration was performed using specific anatomic landmarks with Register software (http://www.bic.mni.mcgill.ca/software/). Up to 10 predetermined anatomic landmarks such as central gyrus and cerebellopontine angle were chosen. A 3×3×3 linear transformation matrix was created and resample of the source image was performed. To achieve optimal coregistration, the b1000 image of DWI was used to coregister with the final T2 image and the perfusion image.

#### Pattern Assessment

Assessments were performed by two independent neurologists blinded to the clinical details. The classical pattern was defined as the core of the infarct (DWI) being completely or majority confined within the perfusion lesion or, in other words, an annular pattern (Figure 1). Other patterns were categorized as nonclassical (Figure 2), such as dissociation between DWI and PWI lesion. All axial slides of the mismatch pattern were assessed. A calibration session was conducted before assessment.

#### Mismatch Volume Calculation

The mismatch volume was the region of PWI volume (Tmax 2 seconds), which was not overlapped by the DWI volume when they were coregistered.

#### Proportion of Mismatch Volume to Core Volume

The proportional of mismatch volume to the core (DWI) volume is calculated by the following formula:

\[
\frac{\text{Mismatch volume}}{\text{DWI volume}} \times 100
\]
Vessel Patency and Location assessment

The patency of the ipsilateral MCA was assessed and rated according to the thrombolysis in myocardial infarction trial flow grade classification as patent (thrombolysis in myocardial infarction classification 3) or any occlusion (thrombolysis in myocardial infarction classification 0 to 2). The location of the DWI infarct core was divided into superficial and deep MCA territory.

Statistical Analysis

Statistical analyses were performed on a commercial statistical software package STATA 10 (STATA Corp). The level of agreement between 2 independent assessors was assessed by weighted kappa score and further confirmed by intraclass correlation coefficient and concordance coefficient. Because of the non-normal distribution of data (significant Shapiro-Wilk test), Wilcoxon–Mann–Whitney 2-sample rank-sum test was used to assess the statistical differences in various characteristic between the classical and nonclassical patterns.

The patients were stratified into 5 time cohorts 0 to 3, 3 to 6, 6 to 12, 12 to 24, and 24 to 48 hours from stroke onset. To assess the unadjusted influence of time to MR scan from stroke onset on the proportion of the classical and nonclassical patterns, both Cochrane-Armitage \chi^2 test for trend and logistic regression (log(time) as the independent variable and the patterns as dependent variable) were used. To assess the unadjusted individual influences of MCA patency and core location on the proportion of the classical and nonclassical patterns, \chi^2 test for proportions was used. The strength of associations was quantified with Spearman correlation coefficient.

The influence of time to MR scan from stroke onset on the proportion of the classical and nonclassical patterns, adjusted for MCA patency, core location, and mismatch volume, was assessed with a logistic regression model.

Results

Patients

There were 93 patients enrolled and were studied with MR, 19 patients had no significant PWI/DWI mismatch, and 7 patients had non-MCA stroke. Remaining 67 patients had median age of 74.0 years (IQR, 67.0, 80.0 years) and range of 19 to 91 years. The median time to MRI scan from stroke onset was 6.2 hours (IQR, 3.0, 21.0 hours), with a range of 2.0 to 48.0 hours. The median NIHSS was 7.0 (IQR, 4.0, 15.0; Table 1). Of these 67 patients, 35 had follow-up T2 scan at \approx 3 months from stroke onset.

Agreement Between Assessors of Mismatch Patterns

Excellent agreement was achieved between the 2 assessors with Cohen kappa score of 0.821 (95% CI, 0.685–0.957) and confirmed by intraclass correlation coefficient of 0.823 (95% CI, 0.73–0.89) and Lin concordance coefficient of 0.823 (95% CI, 0.74–0.9).

Mismatch Patterns

Of the 67 patients, 33 had a classical pattern and 34 had a nonclassical pattern. The median age was 77.0 years and 73.0 years respectively, \((P=0.66)\). The initial median NIHSS was \(7.0\) for both pattern groups \((P=0.075)\).

Mismatch Volumes

The classical patterns had a significantly higher median mismatch volume (62.0 mL) compared to the nonclassical pattern (3.5 mL; \(P<0.0001\)), with mean mismatch volume 78.0 mL and 20.2 mL, respectively. The proportion of mismatch tissue to core volume was significantly larger in classical pattern (367.0%; \(P=0.007\); Table 1).

Tmax Within DWI Lesion

The median Tmax values of the DWI lesions of classical and nonclassical patterns were 8.0 seconds and 3.9 seconds, respectively \((P<0.0001;\) Table 1). The median Tmax values of the region of DWI not overlapped by PWI lesion were 2.2 seconds and 2.2 seconds, respectively \((P=0.25)\), with the range of 1.7 to 3.6 seconds.

Time and Pattern

The median time to MR scan from stroke onset was significantly shorter for the classical pattern (3.4 hours; IQR, 2.5–10.8 hours) compared to those of the nonclassical pattern (10.4 hours; IQR, 4.2–26.1 hours; \(P=0.004\); Table 1). There was a reduction of the proportion of classical pattern over time from 75.0% at 0 to 3 hours to 25.0% at 24 to 48 hours \((\chi^2\text{ for trend slope of } -0.122; \ P=0.005)\), with odds for
classical pattern halving every log (hour) (OR, 0.5; 95% CI, 0.3–0.83; \( P = 0.008 \)).

MCA Patency and Core Location
There is significant difference in the number of patients with MCA occlusion between the classical and nonclassical patterns (Table 3; \( P = 0.0002 \); Spearman rho = 0.434) and similarly for the core location (Table 3; \( P = 0.018 \); Spearman rho = 0.289).

**Time and Pattern Adjusted for Vessel Patency, Location, and Mismatch Volume**
Logistic regression analysis (Table 4) demonstrates significant influence of time on the pattern (OR, 0.48 [per log (hour)]; \( P = 0.047 \); 95% CI, 0.23–0.99) when adjusted for MCA occlusion, mismatch volume, and core location. There are significant relationships between pattern and MCA occlusion (OR, 6.18; \( P = 0.015 \); 95% CI, 1.42–26.88), pattern and mismatch volume (OR, 1.03 [per mL of volume]; \( P = 0.001 \); 95% CI, 1.01–1.06), and pattern and location (OR, 13.9; \( P = 0.018 \); 95% CI, 1.57–123.1), with all other variables being equal.

**Discussion**
We have shown that the classical concept of the MR DWI/PWI mismatch with the preservation of an annular pattern of mismatch surrounding the infarct core is present in \( \approx 49.3\% \) of cases overall during the first 48 hours after stroke onset and it was most commonly seen early after stroke onset. In other words, the classical mismatch pattern fragments with time. Perhaps as a reflection of this early appearance of the classical pattern, the absolute and relative mismatch volumes were greater among classical penumbral cases with larger proportion of penumbral tissue than their nonclassical counterparts. Using a logistic regression analysis, we showed that earlier time points, MCA occlusion, superficial core location, and large mismatch volume were independent variables for the presence of classical pattern.

| Table 1. Summary of All Patients and Classical and Nonclassical Pattern Data |
|-----------------|----------------|----------------|
|                  | All Patients  | Classical Pattern | Nonclassical Pattern |
| N                | 67            | 33              | 34              |
| Male:female      | 42:25         | 18:15           | 24:10           |
| Age, yr          |               |                 |                 |
| Median (IQR)     | 74.0 (67.0–80.0) | 77.0 (69.0–81.0) | 73.0 (63.8–77.5) |
| Time to MRI scan from stroke onset, hr |
| Mean             | 12.9          | 9.1             | 16.6            |
| SD               | 13.8          | 11.5            | 15.0            |
| Range            | 2.0–48.0      | 1.5–45.0        | 2.0–48.0        |
| Median (IQR)     | 6.2 (3.0–21.0) | 3.4 (2.5–10.8)  | 10.4 (4.2–26.1) |
| Initial NIHSS    |               |                 |                 |
| Mean             | 9.8           | 11.5            | 8.1             |
| SD               | 7.2           | 8.0             | 6.1             |
| Range            | 1.0–27.0      | 2.0–27.0        | 1.0–23.0        |
| Median (IQR)     | 7.0 (4.0–15.0) | 7.0 (5.0–20.0)  | 7.0 (3.0–11.5)  |
| Proportion of penumbral volume to infarct core volume, % |
| Mean             | 1951.7        | 3577.3          | 374.0           |
| SD               | 9621.5        | 13601.9         | 730.6           |
| Range            | 2.5–77 876.1  | 23.4–77 876.1   | 2.5–3811.8      |
| Median (IQR)     | 174.1 (44.8–700.0) | 367.0 (85.6–1125.1) | 93.5 (14.1–394.7) |
| Mismatch volume, mL |
| Mean             | 48.7          | 78.0            | 20.2            |
| SD               | 56.3          | 58.2            | 37.0            |
| Range            | 0.3–198.7     | 0.6–198.7       | 0.3–190.5       |
| Median (IQR)     | 31.7 (3.2–72.8) | 62.0 (34.5–116.0) | 3.5 (2.2–23.0) |
| DWI Tmax values, sec |
| Mean             | 6.8           | 8.6             | 4.6             |
| SD               | 3.5           | 3.0             | 2.9             |
| Range            | 1.9–15.2      | 2.6–14.1        | 1.9–15.2        |
| Median (IQR)     | 6.3 (3.6–8.7) | 8.0 (6.6–10.9)  | 3.9 (2.2–6.4)   |
The classical picture of the ischemic penumbra was developed in experimental animals. In PET studies the range of cerebral blood flow values for the infarct core and the ischemic penumbra applied to static models. In reality, a constant evolution of the topography was occurring with time. This has been shown using the permanent MCA occlusion model with PET in baboons with infarct evolution time. This has been shown using the permanent MCA occlusion model with PET in baboons with infarct evolution from deep to cortical territory. This was similar to our occlusion model with PET in baboons with infarct evolution time. This has been shown using the permanent MCA occlusion model with PET in baboons with infarct evolution from deep to cortical territory.

In humans the ischemic process that occurs is much less controlled and is subject to a number of more random events. Vessel occlusion is commonly embolic, either artery to artery or cardioembolic, with clots of varying sizes, ages, and composition. This leads to more random locations of vessel occlusion with consequent differences in vulnerability of tissue (particularly between white and gray matter) and degrees of collateralization from neighboring vessels. Examples of this phenomenon are shown in Figure 2 with dissociation between the core and perfusion defect. Similar to our nonclassical or fragmented pattern, studies have shown that the deeper perforating branches-related infarction had dissociated perfusion defect along with patent proximal MCA. Such dissociation could be attributable to partial reperfusion or embolic events or even apparent vessel patency attributable to poor magnetic resonance angiogram image resolution. Given this relatively random state of affairs compared to the controlled experimental conditions described earlier, the fragmentation of the classical infarct core and penumbral relationship with time can be readily understood.

Further explanations for the breakdown in the classical penumbral pattern may be attributable to the nature of the tissue identified by the DWI lesion. PET has demonstrated that the DWI lesion had quite heterogeneous metabolic characteristics, with some areas consistent with penumbral tissue. The Tmax values of the DWI lesions in nonclassical pattern were lower than classical pattern and would suggest partial reperfusion of these tissues, which is in accord with the higher vessel patency rate of the nonclassical pattern and similar to the result of a study.

A more precise study of the topographical distribution of the ischemic penumbra has been undertaken before, but using a different approach. Markus et al. used 18F-FMISO PET to identify hypoxic tissue and showed that in patients with MCA territory ischemia the salvageable tissue was distributed mainly superiorly, mesially, and posteriorly. Using 15O2 PET and MRI, Guadagno et al. demonstrated penumbra tissue located in the dorsal and ventral most region of the MCA, which has a similar resemblance to the nonclassical pattern in patient 4 in Figure 2.

Using logistic regression we showed that early time, MCA occlusion, superficial core location, and large mismatch volume were independent variables for the presence of classical pattern (Table 2). It can be readily understood that an early MCA occlusion could result in a large region of ischemia, with small core volume in the superficial cortical region resembling the classical pattern with the potential of evolution into nonclassical pattern attributable to complex and somewhat random reperfusion in different locations after the passage of time.

Our study has a number of limitations. First, the visual classification of the 2 patterns was a subjective assessment that may lead to bias, although the agreement between the assessors was excellent. A more objective mathematical assessment of the location and degree of DWI/PWI overlap would be an alternative approach. Second, slice thickness differences between DWI and PWI may lead to slight inaccuracies in coregistration. However, careful manual coregistration was used to overcome these issues and given the close DWI/PWI scan times, patient movement was negligible. Third, a relative Tmax plus 2 seconds may be an alternative approach. Second, slice thickness differences between DWI and PWI may lead to slight inaccuracies in coregistration. However, careful manual coregistration was used to overcome these issues and given the close DWI/PWI scan times, patient movement was negligible. Third, a relative Tmax plus 2 seconds may.
incorporate benign oligemic tissue. A recent study showed absolute Tmax 5.4 seconds represent the ischemic penumbra.\textsuperscript{19} However, this will mainly affect the volume of the perfusion lesion but not its location; hence, the patterns would remain unchanged. In addition, Tmax using singular deconvolution might be sensitive to proximal vessel occlusion and result in inaccurate estimation of the perfusion defect. A tracer arrival insensitive method might minimize this problem. Delay and dispersion problem can also affect the accuracy of perfusion map using Tmax and the temporal resolution of the time bolus curve might not be optimal. Although we were able to demonstrate the effect of time on the distribution of the patterns by using time cohorts, a longitudinal assessment of individual patient’s pattern would be more appropriate. Last, the median NIHSS of both patterns was 7.0, which was relatively low and the result of this study may not be generalizable to more severe strokes.

From our study we have provided the basis for a biologically credible model beyond the classical concept for penumbral tissue that takes into account its topography. Because the divergence from the classical model increases with time, if we are to consider patients for inclusion into clinical trials with longer time windows, then mismatch topography, mismatch volume, core location, and MCA patency may need to be taken into account.

Sources of Funding
Dr Ma has received Postgraduate Medical Research Scholarship from the National Health and Medical Research Council (NHMRC) of Australia. Dr Ma was a recipient of the CardioVascular Lipid (CVL) grant from Pfizer Australia (2005).

Disclosures
None.

References
Fragmentation of the Classical Magnetic Resonance Mismatch "Penumbral" Pattern With Time

Henry Ma, Jorge A. Zavala, Hock Teoh, Leonid Churilov, Marveyles Gunawan, John Ly, Peter Wright, Thanh Phan, Shuji Arakawa, Stephen M. Davis and Geoffrey A. Donnan

Stroke. 2009;40:3752-3757; originally published online October 22, 2009;
doi: 10.1161/STROKEAHA.109.555011

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/12/3752