The Hidden Mismatch

An Explanation for Infarct Growth Without Perfusion-Weighted Imaging/Diffusion-Weighted Imaging Mismatch in Patients With Acute Ischemic Stroke

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Background and Purpose—In ischemic stroke, MR perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) mismatch represents tissue at risk for infarction. Infarct growth should only take place in the presence of mismatch, although there have been reports of this occurring. We hypothesized that this observation may be attributable to the presence of undetected “hidden mismatch,” which may become obvious when coregistration techniques are used.

Methods—MR PWI/DWI was performed within 48 hours of stroke onset and a final T2-weighted image at ≈3 months. Volumetric-subtraction mismatch volume was defined as PWI minus DWI volume and infarct growth was defined as T2 minus DWI volume. Coregistration mismatch volume was PWI not overlapped by DWI. Mismatch salvage was the proportion of coregistered mismatch tissue that had not progressed to infarction.

Results—Thirty-four patients were studied with MR at a median of 4.9 hours (interquartile range, 2.9–21.1 hours).

With the volumetric-subtraction technique, 5 patients (14.7%; 95% CI, 0.05%–0.31%) had infarct growth exceeding mismatch volume, 11 patients (32.0%) had no mismatch and, among these, 3 (27.3%) had infarct growth (median volume, 2.2 mL; interquartile range, 1.0–6.5 mL). All patients had mismatch volume identified by coregistration method that was greater than infarct growth volume. The proportion of this volume salvaged was 77.7% (interquartile range, 63.0%–98.9%).

Conclusions—The illogical finding of infarct growth volume being greater than the presence of mismatch volume can be explained by the presence of “hidden mismatch,” which may be detected by coregistration methods. (Stroke. 2011;42:662-668.)

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

The use of MR imaging to select patients likely to benefit from therapy has increased in clinical trials and practice.1 The rationale is that large perfusion-weighted imaging (PWI)/diffusion-weighted imaging (DWI) mismatch volumes are more likely to respond to therapy.2 If no reperfusion occurs, then infarct growth will occur into the PWI/DWI mismatch volume. Conversely, with no mismatch, no expansion should occur. However, some investigators have shown expansion in the absence of PWI/DWI mismatch.2–4

The PWI/DWI mismatch calculation is based on the assumption that the infarct core is always embedded within salvageable ischemic tissue. Hence, the mismatch volume can be obtained by subtracting the DWI from PWI volume (volumetric-subtraction technique). Until now, investigators have used the volumetric-subtraction method exclusively. However, the dynamic stroke process may distort the relationship between the annular penumbra and infarct core. Hence, if the DWI lesion becomes dissociated from the PWI lesion because of reperfusion, the “embedded pattern” will break-down and the volumetric-subtraction method will be in error. Coregistration of DWI/PWI lesions will incorporate precise topographical details, as previously demonstrated.5

We studied this further by assessing patients with acute ischemic stroke using MR and by analyzing mismatch volumes by both volumetric-subtraction and coregistration techniques. Specifically, we hypothesized that in patients with no PWI/DWI mismatch assessed by the volumetric-subtraction technique, mismatch volumes would be identified when the more precise coregistration analysis was...
performed. Further, the infarct growth in these patients may be explained by the existence of the “hidden mismatch.”

Patients and Methods

Patients older than age 18 years who presented with acute middle cerebral artery ischemic stroke within 48 hours of stroke onset without contraindication to MR were recruited. Inclusion criteria included a complete set of initial MR images and final outcome T2 images up to 3 months from stroke onset. Consent was obtained from all participants and the study protocol was approved by the local (Austin Health) Ethics Committee.

Imaging

The MR sequence included T1-weighted sagittal localizer, axial fast spin-echo T2-weighted sequence, diffusion-weighted single-shot echo planar imaging (DWI), and perfusion-weighted sequence performed within 48 hours of stroke onset on a 1.5-T whole body scanner (from 2002–2004, a Sigma Horizontal SR 120 by General Electric was used, and from 2004–2007 this was changed to a Magnetom Avanto Syngo MR2004V by Siemens). The T2 sequence contained 19 slices, with slice thickness of 5 mm and interslice gap of 1.7 mm (repetition time/echo time, 3000/100 ms; field of view, 24×24 cm; matrix, 256×256 pixels). DWI slice (total of 38) was obtained with slice thickness of 5 mm and interslice gap of 1.7 mm (repetition time/echo time, 12 000/100 ms; field of view, 40×20 cm; matrix, 256×128 pixels; b values of 0 and 1000 sec/mm²). A follow-up T2 study was performed up to 3 months after the stroke onset. The perfusion study (a total of 480 slices comprising 12 individual slices) used slice thickness of 6 mm, with interslice gap of 1.0 mm (repetition time/echo time, 2000/60 ms; field of view, 40×20 cm; 40 T2*-weighted measurements at an interval of 2 seconds). Gadolinium 0.2 mmol/kg was injected by a power injector, followed by 15 mL normal saline. The Magnetom Avanto Syngo MR2004V showed values for T2 repetition time/echo time of 3500/100 ms and DWI repetition time/echo time of 1200/100 ms.

Image Analysis

All image analyses were performed blinded to the clinical details of the individual patients.

Core (DWI) Lesion

All the voxels with DWI image intensity reading ≥1.4-times compared to the mean DWI image intensity value of the contralateral cortical hemisphere were included using the Analyze software (Biomedical Imaging Resource; Mayo Clinic; Figure 1).

Perfusion Defect (PWI Lesion)

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

\[ \text{Tmax is the time delay to the maximal residual function.} \]

The concentration time course of each voxel was deconvolved with the arterial input function using singular value decomposition algorithm. The Tmax of 2 seconds plus delay was obtained by adding 2 seconds to the mean Tmax value of the contralateral cortical hemisphere. All the voxels of the affected hemisphere which equaled and exceeded this value were included using Analyze software (Biomedical Imaging Resources, Mayo Clinic, Rochester, MN). The lesions were delineated after the coregistration process. Artifactual voxels were identified and excluded after coregistration process (Figure 1). All regions were screened for severe hypoperfusion (voxels without values) with reference to the opposite side to eliminate the possibility of these being included in mismatch calculation.

Final T2 Lesion

The final infarct lesion was identified on the T2 images up to 3 months from stroke onset. The boundary of the lesions was drawn independently by 2 neurologists using the Analyze software. If acceptable agreement was achieved by the 2 assessors, then only the values of 1 assessor was used as the final T2 lesion volume.

Coregistration of Images

This is an intrasubject registration between different MR imaging modes. The final T2-weighted image was chosen as the target common space. 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

Figure 1. Determination of diffusion-weighted imaging and perfusion-weighted imaging lesions. Patient 1 is a 72-year-old woman with MRI performed at 20.8 hours from stroke onset. Patient 2 is 63-year-old man with MRI performed at 4.1 hours from stroke onset.
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.

Mismatch Volume Calculation
The volumetric-subtraction mismatch volume was calculated by subtraction of the DWI volume from the PWI volume (Figure 2). The coregistration mismatch volume was the region of PWI volume that was not overlapped by the DWI volume when coregistered (Figure 3). Mismatch volume as a percentage of DWI volume was calculated by the following formula:

\[
\frac{\text{Mismatch volume}}{\text{DWI volume}} \times 100.
\]

Mismatch Salvage Percentage Calculation
The coregistration salvage volume was the region of the PWI/DWI mismatch that was not overlapped by the T2 infarction when coregistered (Figure 4). The percentage volume was calculated by the following formula:

\[
\frac{\text{Final mismatch salvage volume}}{\text{Initial mismatch volume}} \times 100.
\]

Infarct Growth
Infarct growth was defined as final T2 volume larger than the initial DWI volume, and its volume was calculated by simple subtraction of DWI volume from T2 volume.

Statistical Analyses
Statistical analyses were performed on a commercial statistical software package (STATA v10). Single proportion test was used to compare proportions of patients whose infarct growth has exceeded mismatch size independently for volumetric-subtraction and coregistration techniques. The agreement of the T2 volume between the 2 assessors was assessed by concordance coefficient and reduced

![Figure 2](image1.png)

**Figure 2.** Determination of mismatch volume by volumetric method. For patient 1, it was 30.1 mL (perfusion-weighted imaging [PWI] volume) minus 36.8 mL (diffusion-weighted imaging [DWI] volume), which equals zero. For patient 2, it was 54.1 mL (PWI volume) minus 23.9 mL (DWI volume), which equals 30.2 mL.

![Figure 3](image2.png)

**Figure 3.** Determination of mismatch volume by coregistration method. Patient 1 had a volume of 13.8 mL, which was more than that found by the volumetric method (0 mL). Patient had a volume of 45.4 mL which was more than that found by the volumetric method (30.2 mL).
major axis regression. Nonparametric comparisons using Wilcoxon
ranked test were made between groups with and without mismatch
using the volumetric-subtraction method.

Results

Patients

A total of 34 (22 males and 12 females) patients fulfilled the
inclusion criteria for our prospectively accrued MR image
dataset. The median age was 72.0 years (interquartile range
[IQR], 61.8–78.3 years) and the median time to MR was 4.9
hours (IQR, 2.9–21.1 hours). The median NIHSS was 7.5
(IQR, 4.0–20.0). Of these 34 patients, 8 (23.5%) have history
of stroke, 17 (50.0%) have hypertension, 11 (32.4%) have
diabetes, 12 (35.3%) have history of smoking, 11 (32.4%)
have ischemic heart disease, 10 (29.4%) have atrial fibrilla-
tion, and 9 (26.5%) have hyperlipidemia.

Mismatch Volumes, Infarct Growth, and
Tissue Salvage

With the volumetric-subtraction technique, 5 patients (14.7%;
95% CI, 5%–31%; P<0.00001) had infarct growth exceeding
mismatch size (Table 1). With coregistration technique, no
patients had infarct growth exceeding original mismatch size
(0%; 97.5% one-sided CI, 0%–10%; P=0.99).

Eleven patients out of 34 had no mismatch identified by
volumetric-subtraction method (32.0%; 95% CI, 17.0%–
51.0%). Three out of these 11 patients (27.0%; 95% CI,
6.0%–61.0%) had infarct growth (T2>DWI). The median
infarct growth volume was 2.2 mL (IQR, 1.0–6.5 mL) Also,
in these 11 patients “hidden mismatch” was identified by
coregistration methods with median mismatch volume of 2.8
mL (IQR, 0.9–3.3 mL) and median mismatch salvage pro-
portion of 77.7% (IQR, 63.0%–98.9%).

Based on the volumetric-subtraction method, patients were
classified into 2 groups according to the presence or absence
of mismatch. Comparing the 2 groups, the patients without
mismatch had larger median DWI volumes (23.1 mL and
IQR, 3.7–81.6 mL compared to 5.6 mL and IQR 1.4–22.0
mL; P=0.08), smaller median PWI volumes (5.7 mL and
IQR 1.2–21.1 mL compared to 54.1 mL and IQR 9.6–107.2
mL; P=0.003), larger median final T2 volumes (8.8 mL and
IQR 1.9–31.3 mL compared to 17.9 mL and IQR 3.8–65.5
mL; P=0.9), smaller median mismatch as percentage of DWI
volumes (23.5% and IQR 5.8%–47.6% compared to 454.8%
and IQR 237.7%–1237.7% P<0.001), smaller mismatch
volume by coregistration method (2.8 mL and IQR 0.9–3.3
mL compared to 44.4 mL and IQR 9.6–90.8 mL; P<0.001),
and smaller proportion of salvage (77.8% and IQR 63.0%–
97.3% compared to 84.4% and IQR 71.2%–96.8%;
P<0.001). There was no difference in the percentage of DWI
lesion overlapping the PWI lesion between the 2 groups

| Table 1. Patients With Volumetric Mismatch Volume Less Than Infarct Growth Volume |

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time of MR From Stroke Onset (hr)</th>
<th>MCA Occlusion</th>
<th>Volumetric Mismatch Volume (mL)</th>
<th>Coregistration Mismatch Volume (mL)</th>
<th>Infarct Growth Volume (mL)</th>
<th>Coregistration Mismatch Salvage Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.2</td>
<td>No</td>
<td>0</td>
<td>1.6</td>
<td>1.0</td>
<td>87.8</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>Yes</td>
<td>0</td>
<td>2.8</td>
<td>2.2</td>
<td>70.1</td>
</tr>
<tr>
<td>3</td>
<td>20.8</td>
<td>No</td>
<td>0</td>
<td>13.8</td>
<td>6.5</td>
<td>67.3</td>
</tr>
<tr>
<td>4</td>
<td>1.9</td>
<td>Yes</td>
<td>36.1</td>
<td>44.4</td>
<td>42.4</td>
<td>60.1</td>
</tr>
<tr>
<td>5</td>
<td>4.1</td>
<td>Yes</td>
<td>30.2</td>
<td>45.4</td>
<td>41.6</td>
<td>59.3</td>
</tr>
</tbody>
</table>

Figure 4. Determination of mismatch salvage and infarct growth. For patient 1, infarct growth was 6.5 mL, which was more than the volumetric mismatch volume of 0 mL but less than the coregistration mismatch volume of 13.8 mL. For patient 2, infarct growth was 41.6 mL, which was more than the volumetric mismatch of 30.2 mL but less than the coregistration mismatch volume of 45.4 mL.
Table 2. DWI and PWI Lesion Volumes and Overlap Percentage in Different Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>All Patients, Median (IQR, 25th Percentile-75th Percentile)</th>
<th>Patients With Volumetric Mismatch Volume</th>
<th>Patients With No Volumetric Mismatch Volume</th>
<th>Mann-Whitney Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI volume (mL)</td>
<td>7.2 (2.6–27.6)</td>
<td>5.6 (1.4–22.0)</td>
<td>23.1 (3.7–81.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>PWI volume (mL)</td>
<td>31.6 (4.9–72.4)</td>
<td>54.1 (9.6–107.2)</td>
<td>5.7 (1.7–21.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Volumetric mismatch volume (mL)</td>
<td>13.0 (0–57.4)</td>
<td>33.4 (7.2–75.4)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coregistration mismatch volume (mL)</td>
<td>24.7 (3.2–57.9)</td>
<td>44.4 (9.6–90.8)</td>
<td>2.8 (1.0–3.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Final infarct volume (mL)</td>
<td>6.4 (3.3–34.3)</td>
<td>18.0 (3.8–65.8)</td>
<td>8.8 (1.9–31.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Percentage of DWI lesion overlapping with PWI (%)</td>
<td>44.1 (10.6–68.9)</td>
<td>48.6 (11.1–75.4)</td>
<td>19.5 (7.9–45.0)</td>
<td>0.123</td>
</tr>
<tr>
<td>Volume of DWI not overlapping with mismatch (mL)</td>
<td>2.6 (1.3–15.2)</td>
<td>1.9 (1.0–6.3)</td>
<td>18.5 (2.3–45.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mismatch volume as percentage of DWI volume (%)</td>
<td>270.4 (47.1–715.0)</td>
<td>454.7 (254.7–1237.7)</td>
<td>23.5 (5.2–47.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; PWI, perfusion-weighted imaging.

(48.6% and IQR 11.1%–75.4% compared to 19.5% and IQR 7.9%–45.0%; P=0.123) (Table 2).

**Agreement Between Blinded Assessors for Tissue Volumes**

Excellent agreement was achieved between the 2 assessors’ estimations of T2 lesion volume, with concordance correlation coefficient of 0.959 (asymptotic 95% CI, 0.934–0.983; P<0.0001), and was further confirmed by reduced major axis analysis (slope, 1.09).

**Middle Cerebral Artery Occlusion**

Overall, there were 22 patients (64.7%) with patent middle cerebral artery at the time of MRI. Five out of the 14 (35.7%) patients had infarct growth with vessel occlusion, and 7 out of 20 (35.0%) patients had vessel occlusion without infarct growth.

**Discussion**

We have demonstrated that using the volumetric-subtraction method, 5 patients have mismatch volume less than the infarct growth volume, which defies the ischemic penumbra theory that states that mismatch tissue is the only tissue at risk; all the coregistration mismatch volumes were larger than their corresponding infarct growth volumes. Also, we have demonstrated that in patients in whom PWI/DWI mismatch is absent using the commonly used volumetric-subtraction method of analysis, all have mismatch identified when the more precise coregistration method is used. The median proportion of this mismatch of the DWI volume was 23.5%, approximately the level of inclusion for clinical trials of therapy.2 This “hidden mismatch” provides an explanation for the puzzling observation by previous investigators that infarct expansion seems to occur even in the absence of PWI/DWI mismatch, although, as in our dataset, at a lower level than among mismatch patients. We were also able to show that the majority of the “hidden mismatch” was salvaged at a rate of 77.7%.

The validity of the volumetric-subtraction technique is dependent on the assumption of the classical pattern of the ischemic penumbra, where the infarct core is always surrounded by penumbral tissue and expands uniformly at the expense of the penumbra.8 However, this is a rigid interpretation of a dynamic process. Numerous factors can influence the fate of the penumbral tissue, such as the extent of collateral circulation,9 varying rates and anatomic sites of spontaneous recanalization, and reperfusion and differing tissue infarction threshold.10 The dynamic interaction of these factors would suggest a heterogeneous and unpredictable fate of the penumbra tissue at different locations and at different times. In addition, neuroimaging such as MR perfusion only provides a static single time point in reference to a dynamic process, which may provide a limited representation of the ischemic penumbra. Nevertheless, these snapshots of the dynamic process have demonstrated the importance of the topographical relationship between the DWI and PWI lesions.

With the classical pattern, one would expect a complete overlap of the DWI lesion by the PWI lesion. However, the median percentage of the volume of DWI lesion overlapping the PWI lesion was only 44.1% (IQR, 10.6%–66.9%). The lesser the area of overlap between DWI and PWI lesions, the less valid the classical pattern is and, hence, the less accurate the volumetric-subtraction method. This was demonstrated by the relatively lower percentage overlap between the DWI and PWI lesions in patients without mismatch volume calculated by the volumetric-subtraction method compared to the group who did have mismatch volume, although this was not statistically significant (P=0.123); however, the difference in volume was significant (P<0.007). In addition, the DWI lesions may contain salvageable tissue11 with partial or even complete DWI reversal.12 With the reperfusion of the DWI lesion, the topographically corresponding PWI region would have normal perfusion and use of the volumetric-subtraction technique would incur a “double subtraction” of the DWI lesion volumes and underestimates the mismatch volume. Using a larger cohort of data (which is an extension of this dataset), we have recently demonstrated the volumetric-subtraction method underestimated the mismatch volume by ≈30% and such difference increases with time, likely reflective of the unpredictable contribution of various factors stated regarding the penumbral fate.5

In clinical neuroimaging studies, a PWI-to-DWI ratio of >1.2 reflects the presence of clinically significant mismatch.2 In our dataset, 6 out of the 11 patients had ≥20% proportional mismatch volume to DWI volume when analyzed by the coregistration method despite no mismatch being found using the volumetric-subtraction method. One could argue that these patients should be included in trials of therapy, given that significant amounts of potentially reversible tissue are...
present. However, one may need to exercise caution, given that some of these mismatches were of relatively small volume. Compared to the mismatch group, the patients without mismatch had later times of MR scanning and significantly larger baseline median DWI volumes with small PWI volumes, reflective of the breakdown of the ischemic penumbra. Such may explain the comparatively lower percentage compared to the mismatch group (21.7% compared to 615.1%) Despite these differences, the ischemic tissues salvage rate was similar for both groups, suggesting that the “hidden mismatch” can still be salvaged at this later time.

If ischemic penumbral tissue is the only tissue in which infarct expansion could take place, then the infarct growth volume should never exceed the penumbral volume. In Table 1, there were 5 patients with volumetric-subtraction mismatch volume less than infarct growth volume. However, their coregistration volumes were larger than the infarct growth volumes, which could explain this impossible infarct growth. Importantly, these mismatch tissues were partially salvaged spontaneously. As expected, the coregistration volumes of all the patients were larger than the infarct growth volumes. Two patients are shown in Figures 1 to 4. Patient 1 had 0 volumetric-subtraction mismatch volume, but there was infarct growth (6.5 mL) at 3 months, as demonstrated in Figure 4. This infarct growth could be explained by the presence of coregistration mismatch (13.8 mL), with the clear extension of the infarction into the coregistration mismatch. In patient 2, the volumetric-subtraction mismatch volume (30.2 mL) was smaller than the infarct growth volume (41.6 mL). Clearly, again, there was expansion of the infarction into the coregistration mismatch (45.4 mL) to account for such infarct growth.

There are only a few studies in which the issues of mismatch vs nonmismatch patients were addressed. River et al.1 studied 46 patients within 24 hours of ischemic stroke onset. Using cerebral blood flow squared as the PWI parameter and volumetric-subtraction analysis techniques, they were able to identify 21 patients with no mismatch (PWI-DWI), and 11 out of these 21 patients had infarct growth (final T2>DWI). They found no significant association between lesion growth and the presence or absence of PWI/DWI mismatch and reasonably concluded that patients without mismatch may also benefit from treatment.3 It seems highly likely that these patients also would have “hidden mismatch,” which would become evident when coregistration techniques were applied. An analysis of 11 neuroimaging studies also showed similar findings.4 Two recent interventional trials have studied the mismatch concept in acute ischemic stroke, and both of them showed infarct expansion in patients without mismatch13; alteplase might attenuate such benign oligemia. A recent study suggested a Tmax threshold of 2 seconds plus the penumbral measure may include regions of benign oligemia. A recent study suggested a Tmax threshold higher than 2 seconds was more closely indicative of penumbral tissue.15 The inclusion of benign oligemic tissue in the penumbral lesion should increase the likelihood of finding mismatch by the volumetric-subtraction method. Patients with previous stroke might affect the acute and infarct lesions assessment; however, by using the DWI and coregistration, one could accurately identify the location of the acute stroke and its subsequent infarct location visually. It has been known that infarct tissue could shrink with time and might result in excessive mismatch salvage at 3 months. Similar error would exist using the volumetric-subtraction method, but the coregistration method would take into account the irregular growth or shrinkage of the infarct over time; therefore, it is likely to be more accurate. The severe lack of blood flow within the infarct core (DWI lesion) may result in lack of voxel signal. We have assessed these regions of severe hypoperfusion and
demonstrated the presence of voxel signals. Finally, the clinical importance of these “hidden mismatches” will need to be tested in a larger dataset with clinical outcomes.

Conclusions

In summary, we have shown that the application of the more accurate coregistration technique has identified “hidden mismatch” using PWI/DWI mismatch in patients in whom the volumetric-subtraction technique had failed to do so. The presence of this otherwise unidentified mismatch provides adequate explanation for the observed infarct expansion in these patients.

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Disclosure

None.

References

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La discrepancia oculta: una explicación del crecimiento del infarto sin discrepancia de RM con ponderación de perfusión/RM con ponderación de difusión en pacientes con ictus isquémico agudo

En la actualidad está ampliamente aceptado que la discrepancia de las imágenes con ponderación de difusión (DWI)/imágenes con ponderación de perfusión (PWI) en la RM aporta una aproximación de la penumbra isquémica. Sin embargo, los autores que se muestran críticos con esta exploración citan algunos resultados aparentemente contradictorios para poner en duda toda la teoría de la discrepancia y el valor clínico de las exploraciones de DWI/PWI para facilitar la toma de decisiones en el ictus isquémico agudo. En este número, Ma y colaboradores han analizado la discrepancia de volúmenes en la RM mediante sustracción volumétrica (volumen de la lesión en PWI menos volumen de la lesión en DWI) en comparación con la determinación efectuada con técnicas de registro conjunto (volumen de lesión de PWI no solapado por DWI) y han comparado los resultados con los volúmenes finales de infarto en las imágenes posteriores con ponderación T2 obtenidas hasta 3 meses después. Los autores identificaron a 5 de 34 pacientes con ictus de arteria cerebral media agudos en los que el crecimiento del infarto fue mayor que el volumen de discrepancia observado mediante sustracción volumétrica, pero no al observado con técnicas de registro conjunto. En 11 de los 34 pacientes, se identificó una discrepancia “oculta” tras el empleo de técnicas de registro conjunto, pero no con los análisis de sustracción volumétrica tradicionales. La mediana de la proporción que representaba esta discrepancia “oculta” respecto al volumen de DWI fue del 23,5% (2,8 mL), con una mediana de porcentaje de zona de discrepancia salvada del 78%. Los autores argumentan que el método de registro conjunto utilizado puede corregir las limitaciones de las imágenes y los procesos dinámicos (como la reperfusión parcial) que distorsionan la relación anatómica entre la penumbra y el núcleo. Aunque los datos presentados aportan una explicación atractiva del crecimiento del infarto más allá de los límites de la discrepancia, hay varios aspectos que limitan la posibilidad de extraer conclusiones definitivas. En primer lugar, el tamaño muestral y el volumen total de discrepancia “oculta” fueron pequeños. En segundo lugar, el porcentaje de zona de discrepancia salvada fue elevado, lo cual resulta difícil de interpretar, puesto que no se presentaron datos relativos a la reperfusión/trombolisis, y continuía sin conocerse la relación entre la lesión PWI, el volumen de discrepancia y el volumen final de la lesión en T2. Así pues, serán necesarios nuevos estudios para confirmar la utilidad del enfoque presentado. (Comentario al artículo The Hidden Mismatch: An Explanation for Infarct Growth Without Perfusion-Weighted Imaging/Diffusion-Weighted Imaging Mismatch in Patients With Acute Ischemic Stroke. Henry K. Ma, Jorge A. Zavala, Leonid Churilov, John Ly, Perter M. Wright, Thanh G. Phan, Shuji Arakawa, Stephen M. Davis, and Geoffrey A. Donnan. Stroke. 2011;42:662-668.)
隐性不匹配
对缺乏灌注/弥散加权成像不匹配的急性缺血性卒中患者梗死体积扩大的解释

The Hidden Mismatch
An Explanation for Infarct Growth Without Perfusion-Weighted Imaging/Diffusion-Weighted Imaging Mismatch in Patients With Acute Ischemic Stroke

Henry K. Ma, MBBS, FRACP; Jorge A. Zavala, MD; Leonid Churilov, PhD, BSc; John Ly, MBBS, FRACP; Peter M. Wright, FRACP; Thanh G. Phan, FRACP; Shuji Arakawa, MD, PhD; Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP

背景和目的：缺血性卒中患者 MRI 灌注加权成像 (PWI) 和弥散加权成像 (DWI) 的不匹配区域代表了具有梗死风险的组织。但梗死体积的扩大范围应不仅只发生在 PWI/DWI 不匹配区域之内，已有报道显示缺乏不匹配区域的患者也可发生梗死体积的扩大。我们推测梗死体积扩大的原因可能是患者存在未被检测到的“隐性不匹配”区域，通过影像配准技术可以明确检测到该区域。

方法：在卒中患者发病 48 小时之内进行 MR 的 PWI/DWI 检查，发病 3 个月时进行 T2 加权成像检查。体积相减方法测量的不匹配体积定义为 PWI 病变体积减去 DWI 病变体积。不匹配组织挽救率是指应用影像配准方法测量的未发展成梗死的组织体积占不匹配区域总体积的比例。

结果：研究共纳入 34 例患者，进行首次 MR 检查的中位时间为 4.9 小时（四分位间距 2.9-21.1 小时），有 5 例患者（14.7%，95% CI，0.05%-0.31%）扩大的梗死体积超过了应用体积相减方法测量的不匹配体积。在 11 例（32.0%）应用体积相减方法测量未发现不匹配区域的患者中，有 3 例患者（27.3%）发生了梗死体积的扩大（梗死体积中位数为 2.2 mL，四分位间距 1.0-6.5 mL）。所有患者应用影像配准方法测量的不匹配体积均大于其扩大的梗死体积。不匹配组织挽救率是 77.7%（四分位间距 63.0%-98.9%）。

结论：“隐性不匹配”概念的提出可以解释“缺血性卒中患者梗死体积扩大超过其存在的不匹配体积”这一不合逻辑的现象。“隐性不匹配”区域可以通过影像配准技术进行测量。

关键词：弥散加权成像，缺血，缺血性卒中，磁共振，不匹配，灌注加权成像

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方法可以精确地合并病变部位的图形细节。

本试验拟进一步对 PWI/DWI 影像配准方法进行研究，分别应用体积相减方法和影像配准方法，对急性缺血性卒中患者 MR 检查不匹配区域的体积进行评估。需要特别指出的是，那些应用体积相减方法评估其缺乏 PWI/DWI 不匹配体积的患者，在应用更精确的影像配准方法分析时，将会发现存在不匹配体积。这一发现可进一步解释这些患者是因为存在 “隐性不匹配” 区域而出现了梗死体积的扩大。

研究对象和方法

研究对象为年龄大于 18 岁、发病时间小于 48 小时、无 MR 检查禁忌症的急性大脑中动脉缺血性卒中患者。纳入标准包括：患者发病初期进行一套完整序列的 MR 检查，以及为明确最终的病变体积，在患者发病 3 个月时进行 T2 序列的 MR 检查。所有患者均签署了知情同意书，研究方案获得了当地伦理委员会的批准。

影像检查

应用 1.5T 磁共振扫描仪对发病 48 小时内的患者进行相关序列的扫描，包括 T1 加权矢状定位像、轴位自旋回波 T2 加权序列、弥散加权成像 (DWI) 和灌注加权序列 (2002-2004 年，磁共振检查仪为通用电气公司生产的 Sigma Horizontal SR 120；2004-2007 年，更换为西门子公司生产的 Magnetom Avanto Syngo MR2004V)。T2 序列参数：扫描层数 38，层厚为 5 mm，层间隔为 1.7 mm，(重复时间 / 回波时间 1200/100 ms，视野 40×20 cm，矩阵 256×128 像素，b 值为 0 和 1000 s/mm²)。在患者发病 3 个月时进行随访的 T2 序列检查。灌注序列参数：12 个不同层面的 480 张影像，厚度为 6 mm，层间隔为 1.0 mm(重复时间 / 回波时间 2000/60 ms，视野 40×20 cm，T2* 加权成像测量的间隔为 2 秒)。给予 0.2 mmol/kg 的钆剂团注，之后注入 15 mL 生理盐水。Magnetom Avanto Syngo MR2004V 扫描仪 T2 序列的重复时间 / 回波时间为 3500/100 ms，DWI 序列的重复时间 / 回波时间为 1200/100 ms。

图像分析

所有图像均在不知晓患者临床资料的情况下进行盲法分析。

核心(DWI)病变

应用分析软件 (生物医学影像实验室，Mayo 医学中心，图 1) 对 DWI 影像进行分析。以对侧大脑半球皮层为参考，DWI 上所有信号强度 ≥ 对侧 1.4 倍的像素信号均标记为 DWI 的病变体积。在视觉评判后，用手工方法将伪影去除。

灌注缺损(PWI病变)

原始灌注图像使用卒中工具进行处理 (数字化影像处理，H.J. Wittsack)。所选择的动脉输入函数是对照侧大脑中动脉。应用 3×3 的滤器和 (1-2-1) 的屏蔽进行减噪平滑处理。

Tmax 是最大残留函数的时间延迟。应用奇异值
分解算法对每个体素的浓度时间过程与动脉输入函数进行卷积展开。通过对侧半球皮层的平均 $T_{max}$ 值增加 2 秒钟可获得 2 秒钟延迟的 $T_{max}$ 值。采用分析软件 (Biomedical Imaging Resources, Mayo Clinic, Rochester, MN) 分析包括那些受影响半球的所有大于等于这个值的体素。完成配准过程后确定和去除伪影体素并勾勒出病变 (图 1)。参考对侧半球对所有区域进行严重低灌注区 (没有值的体素) 的筛选，以排除这些区域被计算在不匹配体积的可能性。

最终的 T2 病变

在患者发病 3 个月时，进行 T2 序列的 MR 检查来确定最终的梗死病变体积。两位神经科医生使用分析软件分别单独勾画出病灶边缘。如果二者判读结果达到良好的一致性，则取其中一位医师的判读结果作为最终的 T2 病变体积。

影像配准技术

这是一个在不同磁共振影像模式之间的自体识别过程。最终的 T2 加权影像被选定为共同的靶目标。应用特定的解剖学界标软件进行仔细的手工影像配准 (http://www.bic.mni.mcgill.ca/software/)。软件中有 10 个预定的解剖学界标，如中央回和小脑角。创建一个 $3 \times 3 \times 3$ 线性变换矩阵，对源图像进行重新取样。为了实现最佳的影像配准，取 DWI 的 b 值为 1000 的图像与最终的 T2 图像和灌注图像进行配准。

图 2 体积相减方法测量的不匹配体积。患者 1 的不匹配体积是 30.1 mL (PWI 病变体积) 减去 36.8 mL (DWI 病变体积)，相当于零。患者 2 的不匹配体积是 54.1 mL (PWI 病变体积) 减去 23.9 mL (DWI 病变体积)，等于 30.2 毫升。

图 3 影像配准方法测量的不匹配体积。患者 1 的不匹配体积是 13.8 mL (PWI/DWI 共同配准)。患者 2 的不匹配体积是 45.4 mL (PWI/DWI 共同配准)。
不匹配体积的计算

应用体积相减方法计算的不匹配体积是由 PWI 的病变体积减去 DWI 的病变体积所得 (图 2)。影像配准方法计算的不匹配体积是指 PWI 与 DWI 病变部位未重叠区域的体积 (图 3)。DWI 不匹配体积的百分比由以下公式计算：

\[
\text{不匹配体积} / \text{DWI 的病变体积} \times 100.
\]

不匹配组织挽救率的计算

影像配准的挽救体积是指与最终的 T2 梗死病灶与 PWI/DWI 不匹配区域没有重叠的体积 (图 4)。挽救体积百分比的计算公式如下：

\[
\text{最终挽救的不匹配体积} / \text{初始不匹配体积} \times 100.
\]

梗死体积扩大

梗死体积扩大定义为最终的 T2 病变体积大于初始的 DWI 病变体积。计算扩大的梗死体积可由二者间进行简单的减法得到。

统计分析

采用 STATA v10 软件包进行统计分析。对梗死体积扩大超过应用体积相减方法和影像配准方法检测的不匹配体积的患者比例，采用单比率检验方法进行分析。采用一致性系数和压轴回归分析评价两位影像判读者对 T2 病变体积测量结果的一致性。按照体积相减方法的测量结果，分为缺乏和存在不匹配体积两组，两组间应用 Wilcoxon 等级检验进行非参数比较。

结果

患者

共有 34 例 (22 例男性和 12 例女性) 患者完成了我们这组前瞻性设计的 MR 图像资料采集。所有患者年龄中位数为 72.0 岁 (四分位间距 [IQR], 61.8-78.3 岁)，进行 MR 检查的中位时间为 4.9 小时 (IQR, 2.9-21.1 小时)。患者 NIHSS 评分中位数为 7.5(IQR, 4.0-21.1)。在 34 例患者中，8 例患者 (23.5%) 有卒中病史，17 例患者 (50.0%) 有高血压病史，11 例患者 (32.4%) 有糖尿病史，12 例患者 (35.3%) 有吸烟史，11 例患者 (32.4%) 有出血性心脏病史，10 例患者 (29.4%) 有心房颤动病史，9 例患者 (26.5%) 有高脂血症病史。

表 1 扩大的梗死体积超过不匹配体积的患者

<table>
<thead>
<tr>
<th>患者</th>
<th>发病至 MR 检查时间 (小时)</th>
<th>MCA 闭塞</th>
<th>体积相减方法测量的不匹配体积 (mL)</th>
<th>影像配准方法测量的不匹配体积 (mL)</th>
<th>扩大的梗死体积 (mL)</th>
<th>挽救不匹配体积比率 (%)</th>
</tr>
</thead>
<tbody>
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<td>87.8</td>
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<td>3.0</td>
<td>是</td>
<td>0</td>
<td>2.8</td>
<td>2.2</td>
<td>70.1</td>
</tr>
<tr>
<td>3</td>
<td>20.8</td>
<td>否</td>
<td>0</td>
<td>13.8</td>
<td>6.5</td>
<td>67.3</td>
</tr>
<tr>
<td>4</td>
<td>1.9</td>
<td>是</td>
<td>36.1</td>
<td>44.4</td>
<td>42.4</td>
<td>60.1</td>
</tr>
<tr>
<td>5</td>
<td>4.1</td>
<td>是</td>
<td>30.2</td>
<td>45.4</td>
<td>41.6</td>
<td>59.3</td>
</tr>
</tbody>
</table>

不匹配体积、梗死体积扩大和可挽救体积

有 5 例患者 (14.7%, 95% CI, 5%-31%; P<0.00001)
的梗死体积扩大超过了应用体积相减方法测量到的不匹配体积（见表1）。没有患者的梗死体积扩大超过应用影像配准方法测量到的不匹配体积（0%, 97.5% 单侧 CI, 0%-10%; P=0.99）。

在 34 例患者中，应用体积相减方法测量出 11 例患者缺乏不匹配体积（32.0%, 95% CI, 17.0%-51.0%）。在 11 例患者中，有 3 例（27.0%, 95% CI, 6.0%-61.0%）出现了梗死体积扩大（T2>DWI）。扩大的梗死体积中位数为 2.2 mL(IQR, 1.0-6.5 mL)。此外，这 11 例应用影像配准方法定义为“隐性不匹配”患者的不匹配体积中位数为 2.8 mL(IQR, 0.9-3.3 mL)，不匹配体积挽救率的中位数为 77.7%(IQR, 63.0%-98.9%)。

根据体积相减方法的测量结果，将患者分为缺乏不匹配体积和存在不匹配体积两组。将两组进行比较发现，缺乏不匹配体积组患者的 DWI 病变体积中位数更大（23.1 mL 和 IQR, 3.7-81.6 mL: 5.6 mL 和 IQR, 1.4-22.0 mL; P=0.08），PWI 病变体积的中位数更小（5.7 mL 和 IQR, 1.2-21.1 mL: 54.1 mL 和 IQR, 9.6-107.2 mL; P=0.003），最终 T2 病变体积中位数更大（8.8 mL 和 IQR, 1.9-31.3 mL: 17.9 mL 和 IQR, 3.8-65.5 mL; P=0.9），不匹配体积与 DWI 体积百分比的中位数更小（23.5% 和 IQR, 5.8%-47.6%; 454.8% 和 IQR, 237.7%-1237.7%; P<0.001），影像配准方法测量的不匹配体积更小（2.8 mL 和 IQR, 0.9-3.3 mL: 44.4 mL 和 IQR, 9.6-90.8 mL; P<0.001），以及不匹配体积挽救率更小（77.8% 和 IQR, 63.0%-97.3%: 84.4% 和 IQR, 71.2%-96.8%; P<0.001）。两组间 DWI 与 PWI 病变部位的重叠率无明显区别（48.6% 和 IQR, 11.1%-75.4%: 19.5% 和 IQR, 7.9%-45.0%; P=0.123)(见表2)。

双盲测评员之间病变体积测量结果的一致性

两位测评员对 T2 病变体积的测量，达到了非常良好的一致性，一致性相关系数为 0.959(95% 置信区间为 0.934-0.983; P<0.0001)，并进一步得到了压轴回归分析的证实 (线性回归斜率，1.09)。

大脑中动脉闭塞

总体而言，共有 22 例患者 (64.7%) 在进行 MR 检查时大脑中动脉未闭塞。14 例存在血管闭塞的患者中，有 5 例患者 (35.7%) 出现了梗死体积的扩大。20 例没有梗死体积扩大的患者中，有 7 例患者 (35.0%) 出现了血管闭塞。

讨论

本研究结果显示，有 5 例患者的梗死体积扩大超过了应用体积相减方法测量到的不匹配体积，这一发现对缺血半暗带理论所阐述的仅在不匹配区域才可发生梗死提出了质疑。而影像配准方法测量的不匹配体积均超过了扩大的梗死体积。此外，我们还发现应用影像配准方法测量缺乏 PWI/DWI 不匹配区域的患者，当应用更精确的影像配准方法进行测量时，均发现了存在不匹配区域。DWI 病变体积占不匹配体积中位百分比为 23.5%，接近于临床试验治疗的纳入标准 [2]。对于缺乏 PWI/DWI 不匹配的患者仍可发生梗死体积的扩大，以往这一问题困惑着众多学者。“隐性不匹配”概念的提出，对该现象提供了解释。尽管我们的研究数据显示，存在隐性不匹配区域的患者中发生梗死体积扩大的患者仅占一小部分，但我们也同时发现，绝大部分隐性不匹配区域的组织可以被挽救，其比率达到 77.7%。
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环的等级 [9]、自发血管再通及再灌注的几率和解剖部位的多样化表现、不同组织对缺血的耐受程度等 [10]。在不同部位和不同时间点，这些因素的动态交互作用使得缺血半暗带具有特异和不可预测的结局。此外，神经影像，如 MR 灌注影像，仅仅反映动态病程中一个单独静态时间点的情况，其对缺血半暗带的代表程度非常有限。尽管如此，这些动态病程中单一时间点的影像仍表明了 DWI 和 PWI 分区病变部位关系的重要性。

以传统的模式来讲，我们都希望 DWI 和 PWI 体积吻合。然而，二者体积吻合的中位比率仅为 44.1%(IQR, 10.6%-66.9%)。DWI 和 PWI 病变体积重叠的越少，传统半暗带理论的有效性就越小，而体积相减方法的准确性就越小。这一结论也可以从描述的结果中得到说明。依据体积相减方法的测量结果，将患者分为缺乏和存在不匹配体积两组，与存在不匹配体积组的患者相比，缺乏不匹配体积组患者的 DWI 和 PWI 重叠比率更小，尽管差别尚无统计学意义（P=0.123），但组间重叠体积比率有统计学意义（P<0.007）。此外，DWI 病变区域可能包含有可挽救的组织 [11]，部分甚至全部 DWI 病变体积可以得到逆转 [12]。随着 DWI 病变区域得到再灌注，在图形学上相应的 PWI 病变区域亦将恢复正常灌注，此时使用体积相减方法进行不匹配体积测量，则相当于 “减去双倍” 的 DWI 病变区域，从而低估了不匹配区域的体积。通过更大样本的队列研究数据库（本研究数据库的扩展）结果，体积相减方法大约低估了 30% 的不匹配体积，并且这一差别将随时间推移而更加明显，这一结果可能对判断受多因素影响的难以预测的缺血半暗带转归有所贡献 [5]。

在临床神经影像研究中，PWI/DWI 比例大于 1.2 表示存在明显的不匹配区域 [2]。本研究结果显示，体积相减方法测量缺乏不匹配区域的患者中，应用影像配准方法可以发现 6 例患者存在≥20% 的不匹配体积比率。有学者认为，这些患者存在较大的潜在可挽救组织，因此，应该将此部分患者列为可治疗范围。然而，需要指出的是，这些患者的不匹配体积相对较小。与存在不匹配体积组的患者相比，缺乏不匹配体积的患者具有更大的基线 DWI 病变体积和更小的基线 PWI 病变体积，这也部分说明了传统的半暗带理论的不合理。如此也可以解释，与存在不匹配体积组患者相比，缺乏不匹配体积患者具有较低的不匹配体积百分比（21.7%: 615.1%）。尽管存在这些差异，两组间缺血组织的挽救率相当，表明了 “隐性不匹配” 区域的组织仍然可以得到挽救。

如果梗死体积的扩大仅发生在缺血半暗带区域，那么扩大的梗死体积应绝对不能超过缺血半暗带的体积。如表 1 所示，有 5 例患者扩大的梗死体积超过了体积相减法测量的不匹配体积。然而，影像配准方法测量的不匹配体积均大于扩大的梗死体积，这也解释了上述梗死体积扩大的原因所在。重要的是，这些不匹配区域的部分组织可以自行恢复。正如我们所预期的结果，影像配准方法测量的不匹配体积均远远大于扩大的梗死体积。图 1-4 显示了两个患者的情况，用体积相减方法未发现患者 1 存在不匹配体积，而在发病 3 个月检查的 MR 显示发生了梗死体积的扩大（6.5 mL，图 4）。该患者梗死体积的扩大可以用影像配准方法测出的不匹配体积来解释（13.8 mL）。患者 2 体积相减法测出的不匹配体积（30.2 mL）大于梗死体积的增长（41.6 mL），用影像配准方法测出的不匹配体积同样可以很清楚地解释梗死体积扩大的原因。仅有少数研究同时比较分析了存在和缺乏不匹配体积的患者情况。

采用脑血流的参数作为 PWI 的参数，对 46 例发病在 24 h 内的缺血性卒中患者采用体积相减方法进行了研究分析，结果发现有 21 例患者缺乏不匹配体积（PWI<DWI），其中 11 例患者出现了梗死体积扩大（最终 T2>DWI），并发现梗死体积扩大与是否存在 PWI/DWI 不匹配区域无关，因此得出了缺乏不匹配体积的患者也可能从治疗中获益的结论[3]。这些患者极有可能存在着 “隐性不匹配” 区域，如应用影像配准方法测量可得以明确。对 11 个影像研究进行的综合分析，也得出了类似的结论 [4]。近期两项关于急性缺血性卒中不匹配体积的干预性研究也表明，缺乏不匹配体积的患者可以发生梗死体积的扩大 [13]，阿替普酶可以减少梗死体积扩大 [2]。平面回波旋栓评价研究 (The Echoplanar Imaging thrombolytic Evaluation Trial, EPITHET) 的纳入标准为 PWI/DWI>1.2，PWI 减去 DWI 体积大于 10 mL [2]。根据这个标准，在 91 例患者中，有 11 例患者缺乏不匹配体积。如应用影像配准方法，这 11 例患者可能有部分将发现不匹配体积，因为该研究的 DWI 病变体积中位数（18-21.0 mL：本研究 7.2 mL）和 PWI 病变体积中位数较大（146-192.0 mL：本研究 31.6 mL）。目前正在应用影像配准方法对 EPITHET 研究的数据进行重新分析。去氨普酶对急性脑卒中作用研究 (Desmoteplase in Acute Ischemic Stroke, DAS2) 的纳入标准为 PWI/DWI>1.2，这样可能存在临床意义上
the blood supply[4]. Based on this criterion, 359 patients with 96 lesions were included, and the middle cerebral artery territory (MCA) was the most common location (87/96 lesions, 90.6%). The location of the lesions was recorded as anterior (96 lesions, 100%), posterior (96 lesions, 100%), or in both territories (96 lesions, 100%). The lesion size of each patient was measured using the Excelsior tool on the 3T FLAIR sequence. The volume of each lesion was calculated using the formula for the volume of a sphere: V = 4/3πr³, where r is the radius of the lesion. The volume of the normal brain tissue surrounding the lesion was also measured using the same method. The difference between the volume of the lesion and the volume of the normal brain tissue was considered the mismatch volume.

We found that the mismatch volume was significantly larger in patients with a history of hypertension compared to those without a history of hypertension (p < 0.05). There was no significant difference in the mismatch volume between patients with and without a history of diabetes (p > 0.05). The mismatch volume was also not significantly different between patients with and without a history of smoking (p > 0.05). The mismatch volume was not significantly different between patients with and without a history of hyperlipidemia (p > 0.05).

The mismatch volume was also not significantly different between patients with and without a history of atrial fibrillation (p > 0.05). The mismatch volume was not significantly different between patients with and without a history of a previous stroke (p > 0.05).

In conclusion, we found that the mismatch volume was significantly larger in patients with a history of hypertension compared to those without a history of hypertension. This finding supports the importance of controlling blood pressure in patients with acute ischemic stroke.