Regional Cerebral Blood Flow and Magnetic Resonance Spectroscopic Imaging Findings in Diaschisis From Stroke

Wen-Jang Chu, PhD; Graeme F. Mason, PhD; Jullie W. Pan, MD, PhD; Hoby P. Hetherington, PhD; Hong-Gang Liu, MS; Elmer C. San Pedro, MD; James M. Mountz, MD, PhD

Background and Purpose—This study evaluated blood flow and metabolite changes in cerebral diaschisis from internal capsule region infarction using regional cerebral blood flow (rCBF) single-photon emission computed tomography (SPECT) and 1H magnetic resonance spectroscopic imaging (MRSI). We hypothesized that complementary measures of diaschisis effects in white matter (characterized by 1H MRSI) and gray matter (characterized by changes in rCBF) can be measured and exhibit parallel changes.

Methods—Five stroke patients and 16 normal controls underwent Tc-99m hexamethylpropyleneamine-oxime brain SPECT and 1H MRSI at 4.1 T. The metabolites N-acetyl aspartate (NAA) and creatine (Cr) were measured using 1H MRSI. The tissue content was expressed as the percent of gray or white matter in each MRSI voxel to allow comparison of the differential effects of diaschisis in gray and white matter tissue types. The blood flow and metabolite changes were evaluated at superior cerebral regions distant from the stroke to allow a measure of diaschisis relatively unconfounded by their expected changes in the infarction region.

Results—The rCBF SPECT data in stroke patients showed a perfusion defect, with size ranging from 1.23 cc to 10.23 cc, in the region of cortical diaschisis. 1H MRSI showed increased Cr/NAA ratios in regions of white matter diaschisis. There was a tendency for larger rCBF defect size to be associated with greater increases in Cr/NAA values in the same diaschitic cerebral hemisphere, ipsilateral to the infarction.

Conclusion—Diaschisis ipsilateral to stroke in white matter can be characterized by 1H MRSI, and diaschisis ipsilateral to stroke in cortical gray matter regions can be characterized by changes in rCBF. The tendency for greater reductions in cortical rCBF values to be associated with increased Cr/NAA values in the same diaschitic cerebral hemisphere implies that a relationship exists between rCBF reductions in gray matter and abnormal changes in white matter subservient to it. (Stroke. 2002;33:1243-1248.)

Key Words: cerebral blood flow ▪ diaschisis ▪ magnetic resonance spectroscopy ▪ stroke ▪ tomography, emission computed

Diaschisis results in brain dysfunction from neuronal disconnectivity and is a common occurrence after cerebral infarction.1,2 Although diaschisis is believed to be a result of reduction of neuronal activity from axonal damage, the specific molecular and cellular changes that are associated with cerebral diaschisis are not known.3 The relationship between changes in the white matter (WM) and blood flow abnormalities in the gray matter (GM) have not been well characterized. We hypothesize that complementary measures of diaschisis effects in WM (characterized by proton magnetic resonance spectroscopic imaging [1H MRSI]) and GM (characterized by changes in regional cerebral blood flow [rCBF]) can be measured and exhibit parallel changes. The rationale for the study is to perform complementary measurements of stroke-induced diaschisis, using MRSI-measured changes in WM and rCBF changes in GM to provide an interpretation for their corresponding change. In addition, to perform distinctions between WM and GM measurements, we used a method to evaluate diaschisis changes separately, in both WM and GM, using MRI tissue segmentation techniques.

1H MRSI has proven to be a useful technique to map regional changes in cerebral metabolites.4-8 This work characterizes the diaschisis in GM and WM by measuring rCBF and the brain metabolites N-acetyl aspartate (NAA) and creatine (Cr). These data provide complementary information about neuronal damage and CBF in the stroke penumbra and assist in characterizing diaschisis in stroke.9,10

Because of the known heterogeneity of NAA and Cr in GM and WM, variations in metabolite levels can be caused by
pathology or by varying content of GM and WM in the volume of interest.\textsuperscript{11-13} To accurately interpret the MRSI data in stroke patients (especially the relationship between the changes in WM and the resultant metabolite and blood flow abnormalities in GM) requires incorporation of the measurement of tissue content in each MRSI voxel. To achieve this, GM and WM contents in each MRSI voxel were calculated using a previously published method of quantitative tissue segmentation.\textsuperscript{14} After corrections for the metabolite heterogeneities caused by tissue compositions, the \textsuperscript{1}H MRSI data were tabulated with the changes in rCBF. The characterization of metabolite and cerebral perfusion changes resulting from diaschisis may contribute to an understanding of the physiological changes associated with the resolution of diaschisis in the stroke recovery process.\textsuperscript{15}

**Subjects and Methods**

**Subject Population**

All subjects gave informed consent in accordance with our Institutional Review Board guidelines. Sixteen healthy adult volunteers (5 men and 11 women; mean age, 45 years; age range, 20 to 62 years) were recruited from the university community. Five patients with internal capsule region infarction (verified by MR imaging) that resulted in unilateral hemiparesis were evaluated (3 men and 2 women; mean age, 57.2 years; age range, 27 to 72 years). The patients were studied 6 weeks after the internal capsule infarction. Patients were excluded if significant internal carotid artery stenosis (>50% occlusion on either side on cerebral angiography or carotid artery ultrasound) was present or if there was a history of transient ischemic attack. Further exclusion criteria were any other significant central nervous system disease or systemic illness. Using this group of patients with internal capsule region infarction, and studying rCBF and metabolite changes at superior brain levels (above the ventricle, in the centrum semiovale) where the brain was anatomically normal, this study was designed to measure changes in brain regions affected only by diaschisis.

**Tc-99m Hexamethylpropyleneamine-oxime (HMPAO) Single-Photon Emission Computed Tomography (SPECT)**

The 5 stroke patients underwent rCBF brain SPECT on a Picker Triple-Head Gamma Camera (Prism 3000 XP) equipped with low-energy high-resolution collimators after an IV injection of 20 mCi (640 mBq) Tc-99m HMPAO. SPECT data were acquired using 120 projections (40 stops per head) at 45 s/stop and acquiring projection images over 360° at 3° increments. Data were processed into a 128×128 matrix using a Butterworth filter with frequency cutoff of 0.26 Nyquist, order 8, and the Chang algorithm was used for attenuation correction.\textsuperscript{16,17} Every other section was summed in the z direction to yield a transverse SPECT section of 3.92-mm thickness. A reference device (Harrison Medical) was used during the acquisition of SPECT scans to allow coregistration of the transverse sections of all scans, permitting accurate data analysis from identical brain regions of interest (ROI).\textsuperscript{18}

The rCBF defect volume size on SPECT in the area of diaschisis was determined using a previously described method.\textsuperscript{19,20} The SPECT defect volume size in cubic centimeters is given by Equation 1.

\[
V_T = V_p \times \sum_{i=1}^{n} \left( \frac{[M_i - S_i]}{M_i} \right) \times P_i
\]

where \(V_T\) is the total SPECT defect volume size (cc) of the lesion, \(V_p\) is the volume (cc) of the individual voxel, \(S_i\) represents the single-photon emission counts within the abnormal region in the hemisphere ipsilateral to the internal capsule infarction, \(M_i\) represents the single-photon emission counts within the mirrorred region in the contralesional hemisphere, and \(P_i\) is the number of voxels in the ROI; the sum on \(i\) is taken over all scan planes used for calculation of the rCBF defect volume size as described below.

This equation yields a “hypothetical volume of zero perfusion” by comparing the cerebral hemisphere ipsilateral to the internal capsule infarction with the contralateral hemisphere.\textsuperscript{19,20} The hemisphere was compared with the uninvolved hemisphere using 24 circumferential regions (illustrated in Figure 1, A and B), by comparing counts in each ROI with the contralateral brain ROI for the SPECT sections at the level of the MR image section used to obtain the MRSI data. Three SPECT transverse sections were summed to provide a total
 thickness of 11.7 mm, which was compared with the same brain section undergoing MRSI sampling of 10-mm thickness.

**1H MR Image and MRSI Data Acquisition**

All MR data from the 5 patients and the 16 healthy volunteers were acquired using a 4.1-T whole-body MR system with a cavity resonator head coil. Multislice sagittal scout images were acquired using a segmented inversion recovery sequence for the selection of the appropriate transverse plane. A 5-mm-thick axial scout image above the ventricle was then acquired for anatomical references and interpretation of the MRSI data (Figure 2). The spectra in Figure 2 show the metabolites choline (ch), NAA, and Cr (this peak actually represents the total amount of creatine and phosphocreatine) at the chemical shift of 2.02 ppm and 3.02 ppm, respectively. The selected spectra were then analyzed in the frequency domain using NMR software (Tripos Inc), and the line width, chemical shift, and resonance peaks are labeled (right).

Figure 2. Illustration of the localized 1H MR spectra selected from magnetic resonance spectroscopic imaging (MRSI) voxels A and B (voxel size 0.5 cc) in a brain of healthy volunteer (left). Spectrum A was selected from the white matter (WM)-dominated voxel A containing 5.6% GM, and spectrum B was selected from the gray matter (GM)-dominated voxel B containing 88.2% GM. The gray matter content (%GM) in each voxel was quantitatively measured using T1-based tissue segmentation. The resonance peaks are labeled (right).

Quantification of 4.1-T Metabolite Abnormalities in Stroke Patients

Using the statistical images, an ROI circumscribing those voxels with a probability value less than 0.05 was drawn. A mirrored image of this ROI about the midline to the uninvolved contralateral hemisphere was also drawn to provide a control region. The ROI are shown by the fusion image (Figure 3D). The differences between Cr/NAA in the ipsilateral and contralateral hemispheres were quantified by calculating the total metabolite changes between hemispheres ($\Delta m$) using Equation 2.

$$\Delta m = \left[ \frac{1}{n} \sum_{i=1}^{n} M_i \times P_i \right] - \left[ \frac{1}{n} \sum_{i=1}^{n} M_i \times P_i \right]$$

Equation 2 yields a value representing the total amount of abnormal cerebral metabolites (expressed as the ratio Cr/NAA) in the spectroscopic section analyzed for the stroke (S) hemisphere minus the control hemisphere (N). In the derivation described by Equation 2, the metabolite voxel value ($M_i$) times the number of voxels ($P_i$) is determined using the statistical parameters derived from the linear regression analysis of the voxels from the age-matched volunteer group. 26 To aid in the visualization of the abnormal region, those voxels having probability value less than 0.05 were color coded and superimposed on the scout images for anatomical references and are illustrated by the statistical image (Figure 3C).

**Tissue Content in MRSI Voxels and Statistical Test**

To determine the GM and WM content of each MRSI voxel, quantitative T1 maps were generated using a 3-slice, 9-point inversion recovery imaging sequence with 3-mm-thick planes, spaced by 5 mm center-to-center, as described previously. 14 Each voxel was assigned to the tissue type of GM, WM, or cerebral spinal fluid based on the measured T1 value in the voxel. The percents of GM, WM, and cerebral spinal fluid in each MRSI voxel were further calculated using the point-spread function. The resulting tissue content data were combined with spectroscopic data in each MRSI voxel to correct for the tissue dependence of the metabolites. 13,14

The statistical significance of the differences from normal control values for each of the patient voxels included in the selected ROI was determined using the statistical parameters derived from the linear regression analysis of the voxels from the age-matched volunteer group. 26 To aid in the visualization of the abnormal region, those voxels having probability value less than 0.05 were color coded and superimposed on the scout images for anatomical references and are illustrated by the statistical image (Figure 3C).

Figure 3. Illustration of the method used for quantification of metabolite values. The illustration is from a patient with an infarction involving the left internal capsule region. A, The axial MR scout image shows the level at which the metabolites were measured. B, Illustration of the fusion image of the scout MR image with an image of creatine/N-acetyl aspartate (Cr/NAA) metabolite ratios. C, The statistical image illustrates the boundary of the ROI at the $P<0.05$ level of metabolite abnormality. An automated ROI (blue contour) was circumscribed for metabolite values at the $P<0.05$ range and mirrored to the right hemisphere. D, Illustration of fusion image with ROIs. As described in the text, the integral of the abnormal metabolite values in the ROI was performed over all metabolite voxels.
summed over all voxels in the ROI to yield the total metabolite change (Cr/NAA ratio). By subtraction, one can calculate the metabolite changes that may be used to quantify the metabolite abnormality in the MR image section attributed to WM diaschisis change, which can now be appropriately related with diaschisis-induced change of rCBF in the cortical ROI in the cerebral hemisphere ipsilateral to the stroke (ie, total metabolite change quantity compared with total blood flow defect volume). This MRSI semiquantitative method is similar to a method previously published to measure the excess radiotracer uptake and is also similar to the method used to calculate the total SPECT defect volume size described above in Equation 1.27

**Statistical Test**

To compare the stroke group and the control group, we used the 2-sample Student’s t test (2-tailed) to examine the mean difference of the metabolites NAA and Cr. The difference was considered statistically significant at \( P < 0.05 \). Statistical analyses were performed using the SPSS statistical package, version 2.03 (SPSS Inc).

**Results**

**Normal Controls and Patients**

The Cr_{GM}/Cr_{WM} ratio in normal controls and patients’ ipsilateral (diaschitic) hemisphere were 1.35±0.09 and 0.75±0.23, respectively (difference significant at \( P < 0.01 \)). The ratio of NAA_{GM}/NAA_{WM} was 0.63±0.20 in the patient group (ipsilateral hemisphere) and 0.92±0.06 in normal controls, respectively (difference significant at \( P < 0.01 \)). Figure 4A shows representative results from a 76-year-old female patient with a left internal capsule infarction. A higher MR image section (Figure 4B, which was used for analysis) was acquired at the level of the centrum semiovale. This brain region was not directly involved with stroke, and it was anatomically normal. A Tc-99m HMPAO brain SPECT scan section at this normal MR image level showed blood flow reduction (Figure 4C). A fusion image of the blood flow and MR scout image illustrates the region of reduced blood flow at the level of the anatomically normal-appearing MR image (Figure 4D).

**Illustration of the Methods Used to Obtain Quantitative Data from the rCBF Images and the MRSI Data**

Figure 5A shows the normal-appearing MR scout image for the same patient shown in Figure 4. The MRI-Cr/NAA fusion image is also shown in Figure 5B. The metabolite value in each voxel was compared with the normal value and color-coded according to the results of the statistical test described in text. C, The Cr/NAA statistical image is shown for \( P < 0.05 \) (red) and \( P < 0.01 \) (yellow).
cited to produce a statistical image for Cr/NAA elevations with $P<0.05$ (Figure 5C). Using Equation 2 described above, a number representing the excess metabolite ratio ($\Delta m$) in the stroke hemisphere was calculated.

Changes in rCBF and MRSI in the Stroke Population
For all 5 stroke patients, the hypothetical volume of zero perfusion and the abnormal values of Cr/NAA measured from rCBF brain SPECT and MRSI were quantitatively determined and summarized in the Table. The Table displays the side of the patient’s stroke (left/right), the MRSI results in diachistic and normal hemispheres, and the resting rCBF brain SPECT defect volume size.

**Discussion**

**Importance of Diaschisis Measurements in Stroke Recovery**
Diaschisis often results from strokes causing reduction of neuronal synaptic functions in other areas of the central nervous system distant from the stroke. These remote effects result from deafferentation. Diaschisis resolution has been shown to be an important consideration in the stroke recovery process. Over time, functional recovery occurs as a result of synaptic reactivation of neurons. Although it has been established that a patient’s neurological recovery depends on the resolution of the diachistic component of the stroke, the physiological aspects of diachisis related to this resolution are unknown. Therefore, the physiological and biochemical characterization of diachisis is important to formulate development of stroke rehabilitation protocols that will use measurable parameters of diachisis to assess diachisis change during recovery or predict stroke outcome.

**Relevance of Reduced rCBF in Diaschisis**
The existence of diachisis is most commonly accompanied by depressions of cerebral blood flow extending beyond the anatomical lesion. Recovery of function is associated with restoration of perfusion in regions previously affected by diachisis. In this work, describing measures of diachisis, rCBF is a known sensitive indicator of cerebral physiology in brain regions distant from the infarction, including identification of diachisis. Decreasing resting rCBF may occur as a result of impaired vascular supply (ischemia) or it may reflect reduced neurometabolic activity, such as that resulting from neuronal loss or diachisis.

**Relevance of 4.1T Metabolite Abnormalities in Stroke Patients**
A reduction in the level of total amount of Cr and phosphocreatine (PCr) had been reported in several studies of acute infarction, whereas Cr elevation has been found to be present in gliosis as a result of the increased number of astrocytes that are known to contain a 2- to 4-fold higher concentration of Cr than that found in neurons. The finding in this report of reduction of NAA (GM) /NAA (WM) , which was 0.63<sup>29</sup>,<sup>30</sup>,<sup>31</sup> Another inquiry concerns the reduction in NAA$_{GM}$/NAA$_{WM}$ ratio being 0.63±0.20 in the patient group (ipsilateral hemisphere) as compared with 0.92±0.06 in normal controls. This is explained as resulting from a decrease in the patient’s NAA$_{GM}$/NAA$_{WM}$ ratio being dominated by GM NAA reduction compared with WM NAA reduction. The reduction of NAA in diachisis has been previously reported in the case of cross-cerebral diachisis; however, the mechanism has not been explained. In multiple sclerosis, MR spectroscopy data has demonstrated the reductions in NAA concentrations during active disease. The finding in this report of reduction of
NAA metabolism in diaschisis brings into consideration that there may be axonal metabolism impairment in the active phase of diaschisis (possibly similar to multiple sclerosis) that undergoes repair, possibly associated with glial cell activity leading to reversibility in the reduction and normalization in NAA metabolism. NAA is synthesized in brain mitochondria, and the NAA metabolism is closely associated with neuronal mitochondria damage.\textsuperscript{34,35} This supports an interpretation that NAA metabolism and neuronal mitochondria impairment may play an important role in diaschisis.\textsuperscript{34,35}

Relevance of Complementary Measures of Blood Flow and Metabolite Change

Our findings show a trend for progression of increased perfusion deficit as the change in metabolite ratio of Cr/NAA in the diaschitic hemisphere increases. The neuronal mitochondria and associated NAA metabolism may play an important role in the metabolic change in diaschisis.\textsuperscript{3}

This work investigates the complementary information from changes in rCBF and \textsuperscript{1}H MRSI resulting from diaschisis. The data shown in the Table indicate that the change of \textsuperscript{1}H MRSI in diaschisis may become a useful tool in the characterization of diaschisis. The tendency for greater reductions in cortical rCBF values to be associated with increased Cr/NAA values in the same diaschitic cerebral hemisphere implies that a relationship exists between GM and abnormal changes in WM subservient to it.

Acknowledgments

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References

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