Cerebral Blood Volume in Acute Brain Infarction
A Combined Study With Dynamic Susceptibility Contrast MRI and 99mTc-HMPAO-SPECT

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Background and Purpose—The aim of this study was to correlate the abnormality in cerebral blood volume (CBV) measured by dynamic susceptibility contrast-enhanced MRI with that in cerebral blood flow (CBF) estimated by single-photon emission CT with [99mTc]hexamethylpropylenamine-oxime in patients with acute ischemic stroke.

Methods—Nine patients with unilateral occlusion of either the middle cerebral artery or the internal carotid artery (4 men and 5 women; mean±SD age, 74.4±11.6 years) were studied within 6 hours after stroke onset. The relative CBV (relCBV) and CBF (relCBF) in the lesions were defined relative to the contralateral mirror regions.

Results—In the brain regions with mild (relCBF $\geq$0.60), moderate (0.40≤relCBF<0.60), and severe (relCBF <0.40) hypoperfusion, the mean relCBV values were 1.29±0.31, 0.94±0.49, and 0.30±0.22, respectively. The relCBV was significantly elevated in the brain areas with mild hypoperfusion ($P<0.001$) and significantly reduced in the brain areas with severe hypoperfusion ($P<0.001$). The relCBF was significantly better than the relCBV in predicting the evolution of infarction ($P<0.02$). The probability of evolving infarction for the hypervolemic (relCBV >1.0) regions was significantly lower than that for hypovolemic (relCBV <1.0) regions in the relCBF range between 0.40 and 0.50 ($P<0.02$).

Conclusions—In acute ischemic stroke within 6 hours of onset the CBV can be either increased, normal, or decreased, depending on the severity of hypoperfusion. The increased CBV has a protective effect on evolving infarction. Although the CBF is a better predictor of tissue outcome, the CBV measurement may help detect potentially salvageable brain tissue in the penumbra with compromised blood flow. (Stroke. 1999;30:800-806.)

Key Words: cerebral blood flow • cerebral blood volume • cerebral infarction • magnetic resonance imaging • tomography, emission computed

Perfusion and diffusion MRI in acute cerebral infarction has demonstrated its usefulness in detecting disturbed circulation and ischemic brain injury in a very early stage after the onset of stroke.1–4 Among these techniques, dynamic susceptibility contrast-enhanced MRI (DSC-MRI) measures a sequential change in signal intensity during the passage of a paramagnetic substance (Gd-DTPA) injected into circulating blood.5,6 Because the MRI contrast medium is an intravascular tracer, the DSC-MRI provides a measure of cerebral blood volume (CBV) as the area under the concentration-time curve of the contrast agent. Studies of animal ischemia model7–11 and human acute infarction12–15 have shown a decrease in CBV in the vascular territory of steno-occlusive lesions. Although CBV is a fundamental factor in hemodynamic studies of ischemic brain disorder, few studies have reported the relationship between CBV and cerebral blood flow (CBF) in acute stroke patients.16,17

We performed single-photon emission CT with [99mTc]hexamethylpropylenamine-oxime (99mTc-HMPAO-SPECT) and DSC-MRI in patients with cerebral infarction due to either unilateral internal carotid or middle cerebral artery (MCA) occlusion within 6 hours after the stroke onset. In the present study, we aimed to correlate the abnormality in CBV with CBF in the vascular territory of the occluded artery in an early stage of ischemic stroke. The CBV abnormality was analyzed in relation to the magnitude of hypoperfusion and the development of collateral blood supply. The efficiency to predict the tissue outcome (infarction or non-infarction) by either CBF, CBV, or both parameters was tested. The effect of CBV change on the probability of progressing to infarction was examined.

Subjects and Methods

Patients
Nine patients with acute ischemic stroke (4 men and 5 women; mean±SD age, 74.4±11.6 years) were studied within 6 hours of sudden onset of symptoms using CT, SPECT, and MRI. Three of the patients were also studied by conventional angiography. The time of onset was...
determined by reliable information obtained from the patients themselves or their relatives. All the patients showed a signal loss of either unilateral internal carotid artery (n=1) or MCA (n=8) in MR angiography (MRA). All the patients were treated conservatively. During the follow-up period, a recanalization of the occluded artery, confirmed by either conventional angiography or MRA, was found in 7 patients. Follow-up angiographic studies were not performed on the other 2 patients, but repeated SPECT studies showed hyperemia in the territory of the occluded artery. Informed consent was received from all the patients or their relatives before the study. The study was approved by an institutional review committee. Table 1 summarizes the patient information on neurological deficits; timing of the CT, MRI, and angiography (MRA). All the patients were treated conservatively. During the follow-up period, a recanalization of the occluded artery, confirmed by either conventional angiography or MRA, was found in 7 patients. Follow-up angiographic studies were not performed on the other 2 patients, but repeated SPECT studies showed hyperemia in the territory of the occluded artery. Informed consent was received from all the patients or their relatives before the study. The study was approved by an institutional review committee. Table 1 summarizes the patient information on neurological deficits; timing of the CT, MRI, and SPECT; findings from the initial CT; findings from the relCBV; and location of infarction in the follow-up period.

SPECT Imaging

After neurological examination and CT scanning, CBF imaging was performed by means of a ring type SPECT scanner (Headome SET-080, Shimadzu Co) using 740 MBq (20 mCi) of $^{99m}$Tc-HMPAO. The scanner simultaneously produces 31 tomographic axial images that cover the whole brain. A low-energy, high-resolution collimator was used for data acquisition. Image matrix size was 128×128. A third-order Butterworth filter with a cutoff frequency of 0.05 cycles/cm and a ramp filter were used for image reconstruction. In-plane and axial spatial resolutions of the scanner were 14 and 22 mm full width at half maximum, respectively. The CBF imaging started 10 minutes after the injection of $^{99m}$Tc-HMPAO, and data acquisition continued for 24 minutes. The image slices were parallel to the orbitomeatal (OM) line with a 5-mm interslice distance. Reconstructed images were corrected for tissue absorption using an attenuation coefficient of 0.065 cm$^{-1}$, and for the nonlinear uptake of $^{99m}$Tc-HMPAO in high-flow areas with the method developed by Lassen et al. A previous study validated the accuracy of this correction by comparing the CBF measured by $^{99m}$Tc-HMPAO-SPECT with that estimated by PET with C$^{15}$O. Relative CBF (relCBF) was defined as the total SPECT counts in the lesion divided by the total counts in the mirror region in the contralateral unaffected hemisphere.

MRI

MRI studies were performed using a 1.5-T whole-body superconductive scanner (Magnetom Vision, Siemens Medical Systems). Each study began with a conventional T2-weighted turbo spin-echo sequence (TR=3600 ms, TE=96 ms, number of excitations=1). Nineteen T2-weighted image (T2-WI) slices, which covered the whole brain, were obtained parallel to the anterior commissure-posterior commissure (AC-PC) line with a 6-mm slice interval. One of the T2-WI slices was set at the AC-PC line. The T2-WI was followed by a 3D time-of-flight MRA (TR=39 ms, TE=6.5 ms, flip angle 20°, 20-cm field of view, 1-mm slice thickness, number of excitations=1, 60-mm slab thickness, partition 60, matrix size 128×128). Velocity compensation was performed in the readout and slice-selection directions. A maximum-intensity projection algorithm was used for MRA image reconstruction.

Dynamic Susceptibility Contrast-Enhanced MRI

The DSC-MRI studies were performed with a single-shot gradient-echo planar pulse sequence (TE=54 ms, flip angle 90°, 23-cm field of view, 5-mm slice thickness) after a bolus injection of 0.1 mmol/kg Gd-DTPA. This contrast medium was administered to the antecubital vein over a period of 3 to 5 seconds, followed by the injection of 10 mL saline. Immediately after the administration, the scan was initiated to measure signal intensity change during the first bolus passage of the contrast medium through the brain. We obtained 60 single-shot echo-planar images with a 1-second repetition time for 60 seconds in 5 slices, 1 covering the cerebellum and the other 4 in the cerebrum obtained at 0 mm, 12 mm, 24 mm, and 36 mm above and parallel to the AC-PC line. The image matrix size was 128×128.

After the DSC-MRI, T1-weighted spin-echo images (TR=665 ms, TE=14 ms) were obtained to determine whether the contrast medium leaked into brain parenchyma. By visual inspection, none of the patients showed a parenchymal enhancement.

Calculation of Relative CBV

A total of 300 images acquired in 60 seconds (5 slices per second) were transferred to a Unix workstation (SUN Ultrasparc 20) to create maps of CBV. As previously described, the changes in signal intensity during the bolus passage of the paramagnetic contrast medium correlate with the concentration of the contrast medium in blood. In each pixel, the signal intensity change in 60 seconds before, during, and after the bolus passage of the contrast medium was fitted by a gamma function and
defined as the concentration-time curve. According to the tracer kinetic principles, CBV was defined as the area under the concentration-time curve and calculated by use of the MR Vision software (MR Company). The CBV images were generated at 0 mm, 12 mm, 24 mm, and 36 mm above and parallel to the AC-PC line and at the level passing through the cerebellum. Relative CBV (relCBV) was defined as a ratio of CBV in the lesion to that in the mirror region in the contralateral unaffected hemisphere.

Image Registration

The T2-WI, CBV, and CBF images were transferred to a Unix workstation (TITAN 750, Kubota Computers). Our data analysis requires spatial registration of the T2-WI, CBV, and CBF images. The T2-WI and CBV images were taken consecutively while the subject was in the same position in the scanner. Care was taken to immobilize subject’s head to avoid head movement between scans. Therefore, the T2-WI and CBV images obtained at 0 mm, 12 mm, 24 mm, and 36 mm above and parallel to the AC-PC line are in registration.

The CBF image was registered to the T2-WI using the automatic multimodality image registration (AMIR) software developed by Ardekani et al. In this method, the MR image is first segmented into a number of spatially contiguous connected components using K-means clustering and connected components analysis. Six rigid body parameters (3 translations and 3 rotations) are then found such that when the CBF images are matched to the T2-WI images using these parameters, the total sum of squared deviations from mean CBF within all connected components is minimized (see Reference 21 for details). The accuracy of registration between PET and MR images with this method has been previously estimated to be <3 mm. After the registration procedure, we obtained CBF and CBV images registered to the T2-WI. Figure 1 demonstrates the original CBF image, registered CBF image, fusion of the registered SPECT and T2-WI obtained at the AC-PC line, and the corresponding CBV image.

Data Analysis

The CBV and CBF images registered to the T2-WI obtained at 0 mm, 12 mm, and 24 mm above and parallel to the AC-PC line were selected for analysis. Several 16×16 mm² square shape regions of interest (ROIs) were placed on the CBF images and the corresponding CBV images in the affected hemisphere and in the mirror regions in the contralateral hemisphere as follows: 7 ROIs in the AC-PC line+0-mm image (2 on inferior frontal gyrus, 4 on temporal lobe, and 1 on basal ganglia); 7 ROIs on the AC-PC line+12-mm image (2 on inferior frontal gyrus, 4 on temporal lobe, and 1 on basal ganglia); and 5 ROIs in the AC-PC line+24-mm image (inferior frontal gyrus, precentral gyrus, postcentral gyrus, supramarginal gyrus, and corona radiata). The setting of ROIs is shown in Figure 1. According to their relCBF value, each ROI was classified as a region with mild (relCBF ≥0.60), moderate (0.40 ≤ relCBF < 0.60), or severe (relCBF < 0.40) hypoperfusion. The threshold for these relCBF categories were determined retrospectively. The upper threshold of 0.60 was the highest relCBF among the infarcted brain regions. The lower threshold of 0.40 was the lowest relCBF among the noninfarcted brain regions.

The final location and extension of cerebral infarction was evaluated by an MRI study performed after 7 days or later (mean±SD, 21±10 days) in 7 patients and a CT study (mean±SD, 19±3 days) in 2 patients. The brain region for each ROI in the affected side was classified as infarcted or noninfarcted. The probability of infarction (PI) was defined as the number of ROIs for infarction divided by the number of all ROIs in the relCBF range of 0.40 to 0.50 and 0.50 to 0.60. The PI was analyzed separately for hypervolemic (relCBV >1.0) and hypovolemic (relCBV <1.0) ROIs in the moderate hypoperfusion range.

Statistical Analysis

Mean relCBV values in the brain areas with mild, moderate, and severe hypoperfusion were compared with 1 and statistical significance was determined by the Wilcoxon test. Friedman’s test was used to evaluate a difference in relCBV and relCBF between infarcted and noninfarcted regions. Univariate discriminant analysis was performed to estimate cutoff values that best discriminated between infarction and noninfarction. Multivariate (relCBV and relCBF) discriminant analysis was used to obtain a cutoff function. By using the best cutoff values and function, the sensitivity (true positive rate), specificity (true negative rate), and efficiency to predict the tissue outcome was calculated. Significant difference in the efficiency between relCBV, relCBF, and both parameters was evaluated by a χ² test. Receiver operating characteristic (ROC) analysis was also performed to examine the accuracy of relCBF and relCBV to predict the tissue outcome. The areas under the ROC curves for relCBV and relCBF were calculated and compared with Wilcoxon statistics. Significant difference in the PI between hypervolemic and hypovolemic regions was examined by a χ² test.

Angiographic Evaluation

Three of the 9 patients were studied by conventional 4-vessel angiography immediately after the SPECT and MRI studies. In these patients, the development of leptomeningeal collateral circulation was evaluated by 2 neuroradiologists (J.H. and E.S.) independently.
Results

In the vascular territory of the occluded artery, the mean±SD relCBV values were 1.29±0.31, 0.94±0.49, and 0.30±0.22 for the brain regions with mild hypoperfusion (n=45 regions, mean±SD relCBF =0.77±0.11), moderate hypoperfusion (n=79, 0.48±0.04), and severe hypoperfusion (n=47, 0.28±0.09), respectively. Significant elevation of relCBV was found in the brain regions with mild hypoperfusion (P<0.001).

The mean relCBV was significantly decreased in the brain regions with severe hypoperfusion (P<0.001). Mean relCBV in the brain regions with moderate hypoperfusion was not significantly different from 1. Figure 2 shows the CBF, the CBV, and the follow-up T2-WI in patient 4, who suffered from sudden onset of left hemisensory disturbance and was studied within 5 hours after the onset. The CBV image shows both local decrease and increase in the vascular territory of the occluded right MCA.

Figure 3 illustrates the relationship between relCBV and relCBF in each infarcted (filled circles) and noninfarcted (open circles) region. In the infarcted (n=106) and noninfarcted regions (n=65), mean relCBV was 0.61±0.47 and 1.26±0.37, respectively, and mean relCBF was 0.39±0.12 and 0.69±0.15, respectively. Mean relCBV and relCBF for the infarcted regions were both significantly lower than those for the noninfarcted regions (P<0.01). Figure 4 illustrates a scatterplot of relCBF and relCBV for infarcted (filled triangles) and noninfarcted (open circles) regions. The best cutoff value to discriminate between infarction and noninfarction was 0.52 for relCBF and 0.85 for relCBV. The best discriminant function was z=6.33×relCBF+0.66×relCBV−3.75. Table 2 shows the sensitivity, specificity, and efficiency of discrimination between infarction and noninfarction. The efficiency of relCBF was significantly better than that of relCBV (P<0.02). The efficiency was not significantly improved when both parameters were used for discrimination. The area under the ROC curve for relCBF (mean±SE, 0.90±0.02) was significantly larger than that for relCBV (0.81±0.03, P<0.01).

Mean PI in the hypovolemic regions was 0.96 and 0.58 in the corresponding relCBF ranges, respectively. Mean PI of hypovolemic regions was significantly lower than that of hypovolemic regions (P<0.02) in the relCBF range between 0.40 and 0.50.

Conventional 4-vessel angiography was performed in 3 patients (cases 1, 2, and 5) after the SPECT and MR studies. In patient 1, the blood supply from the left anterior cerebral artery through the leptomeningeal anastomosis was observed in the brain regions with the increased relCBV distal to the occluded MCA. In patient 2, the leptomeningeal collaterals arising from the right paracental artery filled the right central artery in retrograde fashion (Figure 5). In patient 5, the collateral perfusion was not developed. In patients 1 and 2, the retrograde arterial filling was prolonged to venous phase. The capillary blush was not evident.

Discussion

A number of experimental7–11 and clinical MR studies12–15 have demonstrated a reduction in the signal change during the passage of contrast medium in the ischemic core distal to the
showed no detectable parenchymal enhancement, in agreement with the previous reports that parenchymal enhancement was not seen on the day of onset in patients with acute cerebral infarction. The relCBV increase was associated with mild hypoperfusion (relCBF ≥ 0.60), which did not induce an infarction. We therefore concluded that the relCBV increase does not result from the leakage of the Gd-DTPA due to blood-brain barrier breakdown but may represent an altered cerebral hemodynamics after arterial occlusion.

The relCBV increase in the vascular territory of the occluded artery has been found in previous DSC-MRI studies but not correlated with relCBF. The CBV increase has also been found in PET studies in an acute MCA occlusion model of baboons, in patients with acute cerebral infarction, and in patients with chronic internal carotid artery occlusion. The increased CBV has been attributed to a vasodilatation of precapillary resistant vessels against a fall of perfusion pressure. In 2 patients (cases 1 and 2), we could analyze the location and extent of brain regions with raised relCBV in relation to the angiographic features. In both cases, a retrograde filling of the cortical arteries distal to the occluded artery via the leptomeningeal collateral channel was found in the areas corresponding to those with increased relCBV. The transit of contrast medium was delayed. In patient 5, neither the increase in relCBV nor the leptomeningeal collateral perfusion was found in the territory distal to the occluded right MCA. Although the mechanisms for developing collateral circulation are not fully understood, the increase in relCBV may depend on the development of collateral circulation.

Moderate hypoperfusion was defined as the relCBF range between 0.40 and 0.60 where 75% of regions were infarcted and others were not. This relCBF range was similar to the ischemic threshold observed in a large patient population studied within the same time window using 99mTc-HMPAO-SPECT. We speculate that the brain regions in this relCBF range may correspond to an “ischemic penumbra”. The penumbra tissue may consist of both hypervolemic and hypovolemic regions associated with the delayed bolus transit. This view is supported by the recent experimental studies that the hemodynamics in the penumbra was characterized by delays in bolus transit time due to a perfusion through the collateral channels.

Is there any effect of hypervolemia and hypovolemia on evolving ischemic brain damage? Heiss et al. studied the relationship between hemodynamic and metabolic failures in acute cerebral infarction and progressive derangement of peri-infarct viable tissue in humans. In their study, a raised CBV measured within 6 to 48 hours of stroke onset did not contribute to maintaining metabolic activity in the peri-infarct regions. Tomita et al. found “low-perfusion hyperemia” in the ischemia model of cat brain, which followed the initial CBV decrease immediately after MCA occlusion and disappeared within several hours. The low-perfusion hyperemia did not have a protective effect on ischemic lesion evolution. In the present study, however, the probability of progressing to infarction was significantly lower in the hypervolemic regions (PI=0.68) than in the hypovolemic regions (PI=0.96) in the relCBF range between 0.40 and 0.50. Because there was no significant difference in mean relCBF between the hypervolemic (relCBF=0.46±0.02) and hypovolemic regions (0.45±0.02) in this relCBF range,
hypervolemia within 6 hours of stroke onset may reduce the risk for evolving infarction. The protective effect of hypervolemia on evolving infarction was also suggested by Lo et al\textsuperscript{33} in their study of mice lacking endothelial nitric oxide synthase.

Discriminant analysis and ROC analysis indicated that the evolution of infarction can be predicted by the relCBF significantly better than by the relCBV. By employing both relCBF and relCBV, the efficiency in predicting a tissue outcome was not significantly improved. The relCBV measurement, however, may help in distinguishing between the regions at low risk of infarction and those at high risk and detecting potentially salvageable brain regions.

There are several methodological limitations in the present study. First, we used relative measures by taking ratios of CBV and CBF in the lesion to those in the mirror region in the contralateral hemisphere. This normalization assumes that the contralateral hemisphere is unaffected by the unilateral ischemic insult. However, as reported by Meyer et al\textsuperscript{35} there was contralateral hemispheric reduction of CBF, termed “transhemispheric diaschisis,” despite strictly unilateral hemispheric stroke. Therefore, the relCBF may underestimate a severity of hypoperfusion in the territory of the occluded artery. The effect of transhemispheric diaschisis on CBV is another potential source of error. Second, we used \textsuperscript{99m}Tc-HMPAO as a flow tracer. It has been recognized\textsuperscript{36} that hyperfixation of \textsuperscript{99m}Tc-HMPAO occurs in subacute (2 to 3 weeks) ischemic stroke when the infarcted area is reperfused. This may lead to spuriously high estimates of CBF. However, the use of \textsuperscript{99m}Tc-HMPAO may not critically affect main findings of the present study, because our patients were studied within 6 hours after onset and did not show evidence of recanalization in the MRA or conventional angiographic study. Third, there is a difference in spatial resolution between the SPECT and DSC-MRI. Even after image registration, the different magnitude of partial volume averaging and the difference in slice thickness between the SPECT and DSC-MR may inherently limit the accuracy of the CBF-CBV relationship.

The design of the present study also limited the accuracy of the results. First, there is a time interval between the SPECT and MR studies. In 6 patients, the interval was $\leq 1$ hour. In other 3 cases, this was 2.2 to 2.5 hours. The interval between studies may be a source of error, because hemodynamic changes may occur during the first several hours of onset. Second, it is difficult to determine whether the infarction found by the follow-up T2-WI or CT is induced by the initial ischemic event alone.

Despite these limitations, several conclusions could be made. In patients with acute ischemic stroke studied within 6 hours after onset, the relCBV was significantly increased in the noninfarcted area in the territory of the occluded artery. The relCBV increase was associated with the development of leptomeningeal collaterals arising from the right paracentral artery, as indicated by arrowheads.

![Figure 5. A, The CBF image (left), CBV image (center), and left carotid angiography (right) inpatient 2, who suffered from a right MCA occlusion. The relCBF was severely decreased in the territories of right MCA (indicated by a), except for the central artery territory (b), where the relCBV was elevated. The left carotid angiography (antero-posterior view) demonstrated the development of leptomeningeal collaterals arising from the right paracentral artery, as indicated by arrowheads. B, The signal intensity change of the DSC-MRI in region a ( ), region b ( ), and the mirror region of b in the normal hemisphere (circ). The sequential signal intensity in each region was expressed as a percentage of mean signal intensity of the initial 4 DSC-MRI obtained before arrival of Gd-DTPA at the brain. The $16 \times 16$ mm$^2$ square-shape ROIs were used for count reading. The relCBF values in regions a and b were 0.38 and 0.48, respectively. The relCBV values in regions a and b were 0.28 and 1.26, respectively.](http://stroke.ahajournals.org/figs/2000/04-hatazawa-tcm-mfigs/5fig5.png)
indicative of evolving into infarction. The relCBF is a better predictor of infarction than relCBV. The CBV measurement, however, provided the new information that the probability of infarction in the hypovolemic regions is lower than that in the hypervolemic regions. The protective effect of hypervolemia may suggest testable clinical strategies for protection of penumbral tissue.

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