Longitudinal Study of Regional Cerebral Blood Flow Changes in Depression After Stroke

Shuhei Yamaguchi, MD, PhD; Shotai Kobayashi, MD, PhD; Hiromi Koide, MD; and Tokugoro Tsunematsu, MD, PhD

Background: We studied 60 patients longitudinally to examine relations between regional cerebral blood flow and depressive states after stroke.

Methods: Poststroke depressive states were assessed by the Zung Self-Rating Depression Scale (SDS). Regional cerebral blood flow was measured using the $^{133}$Xenon inhalation method with patients in the resting state on the same day as the SDS assessment. All patients were followed for an average of 14 months after the initial assessment.

Results: Severity of depression was inversely correlated with regional cerebral blood flow values in the parieto-occipital regions of the right hemisphere and in the anterior temporal region of the left hemisphere at the initial evaluation. Patients with lesions in left frontal or right parieto-occipital regions were more depressive in comparison with those with other brain lesions. Follow-up study showed significant inverse correlations between changes in SDS score and changes in regional cerebral blood flow at all scalp sites. Furthermore, higher inverse correlations were observed at specific brain regions in each hemisphere, including the parietal and parieto-occipital regions of the right hemisphere and the anterior temporal and inferior frontal regions of the left hemisphere. This relation was independent of recovery from neurological deficits.

Conclusions: These results suggest that dysfunction of specific cortical and subcortical regions in both hemispheres asymmetrically contributes to depressive state after stroke. (Stroke 1992;23:1716–1722)

KEY WORDS • cerebral blood flow • depression • rehabilitation

Depression is one of several specific complications after stroke and exerts a negative impact on the rehabilitation process and outcome of some stroke patients. The relation between the location of the lesion and the occurrence of poststroke depression has been repeatedly investigated, and some cortical and subcortical damage is reported to result in depression. These studies, however, have been inconsistent with regard to location of lesions accounting for depression. Most studies have analyzed patient data obtained from a one-point measurement after stroke and examined the relation between the depressive state and lesion location on the basis of computed tomographic (CT) scans. These studies overlook the time course of depression and effects of the lesion on remote neural structures, which might play an important role in the regulation of affect.

Regional cerebral blood flow (rCBF) studies provide a useful tool for assessing the functional-anatomic basis of poststroke depressive states. It is not unusual for focal CBF and metabolic abnormalities to be present that are remote from the site of the lesion. In such cases, rCBF or metabolic studies could reveal dysfunction of remote neural structures responsible for neuropsychiatric symptoms.

Selective hypometabolism in specific cortical or subcortical regions has been demonstrated in affective disorders with or without associated neurological diseases (i.e., Parkinson's disease and endogenous depression). We hypothesized that specific cortical areas implicated in the modulation of emotion would show significant changes in rCBF in relation to temporal profiles of depressive states after stroke.

Subjects and Methods

Subjects for this study were selected from a cohort of patients with cerebral infarction or hemorrhage who attended the third division of internal medicine at Shimane Medical University. The cohort was composed of 51 men and nine women (64.1±8.6 years old, mean±SD), all of whom met the selection criteria. The following examinations were performed at the beginning of the study: 1) medical and neurological examinations and medical history, 2) blood pressure measurements, and 3) blood sampling for complete blood count and biochemical analysis. Neurological examinations evaluated motor and sensory function, higher cortical function (aphasia, visuospatial neglect, apraxia), cognitive function, and activities of daily living. In the current study, we excluded subjects who had disturbances of consciousness, dementia (less than 20 points on Hasegawa's intelligence score; full scales=32.5 points), or severe aphasia with difficulty in daily conversation, or who had suffered from psychiatric diseases or alcohol-
ism before stroke. We also excluded patients who had already received antidepressant therapy due to severe depression after stroke.

Lesion location was confirmed by CT scan or magnetic resonance imaging; all patients had one or more supratentorial lesions. Twenty-two patients had lesions in the right hemisphere and 20 patients in the left hemisphere. Other patients had bilateral lesions. Lesion size was evaluated by measuring the diameter of lesion on a CT or magnetic resonance imaging film. The severity of depression was quantified by the Zung Self-Rating Depression Scale (SDS) on the day of rCBF measurement. Some patients were also evaluated by the Hamilton Rating Scale for Depression, and the severity of depression was quantified by the Zung Self-Rating Depression Scale (SDS) in 10 patients, and after 1 year in 27 patients. Poststroke duration was calculated as the time after the last stroke episode in patients with multiple stroke attacks. All patients had the final measurement of SDS and rCBF 418±87 days (320–553 days) after the initial evaluation. Neurological examinations, blood pressure measurements, and blood sampling were repeated at the final assessment. No patient was treated with an antidepressant during the follow-up period. No patient showed any new lesions on CT scan or clinical evidence of recurrent stroke during the follow-up period.

Regional CBF was measured by a 133Xe inhalation method with patients in the resting state with eyes closed. This method is noninvasive, reliable, and reproducible. Eight collimated probes were placed on the skull surface of each hemisphere. After a 5-minute resting period during which background gamma activity was measured, approximately 3 mCi of 133Xe gas was inhaled through a face mask for 1 minute, then the decreasing activity of the isotope was monitored on the scalp. End-tidal 133Xe activity was also measured for correction of its recirculation to the brain. The rCBF value (F1 value) was calculated by the Fourier method. The long-term reproducibility of the 133Xe inhalation method in rCBF measurement at our institute has been previously reported. The end-tidal partial pressure of CO2 (Pco2) was monitored by a capnograph, but rCBF was not corrected for Pco2.

Statistical analysis was performed using the Student’s t test, the Pearson correlation coefficient, and the χ² test.

Results
Profile of Mood State
Table 1 shows SDS scores at the initial and final assessments. Fifty percent (n=30) of patients had SDS scores higher than 45 points at the initial assessment. SDS scores in 13 of 30 depressed patients whose score was more than 45 points decreased to less than 45 points during the follow-up period. Ten patients with SDS scores of less than 45 points at the initial assessment had scores of more than 45 points at the final assessment. The presence of motor paresis or sensory disturbance was not associated with high SDS scores. Patients who had extrapyramidal signs or higher cortical dysfunction showed higher SDS scores than patients without those symptoms, but the difference of SDS score was not significant.

Relation Between SDS Score and Regional Cerebral Blood Flow
There was a significant inverse correlation between SDS score and rCBF value at the parieto-occipital region in the right hemisphere and at the anterior temporal region in the left hemisphere at the initial time of study (see Table 2). The mean rCBF of the entire brain showed a trend of inverse correlation with SDS score. The final assessment of SDS score and rCBF showed a trend of inverse correlation between these variables at the localized regions in which a significant correlation was observed at the initial assessment in each hemisphere.

Figure 1 shows the relation between lesion location and SDS score (top panel) and between lesion location and rCBF (bottom panel). This analysis included patients with a unilateral lesion. At the initial assessment, patients with left frontal lesion (n=6) or right parieto-occipital lesion (n=6) had significantly higher SDS scores in comparison with those with lesions at the same region in the opposite hemisphere (right frontal, n=9; left parieto-occipital, n=8). These differences in SDS score were not significant in the final assessment. Patients with subcortical lesions in the right or left hemisphere had comparable SDS scores (left basal ganglia, n=4; right basal ganglia, n=4; left thalamus, n=2; right thalamus, n=3). The mean rCBF value of the entire brain was low in patients with left frontal lesion or right parieto-occipital lesion. These patients had low rCBF values over the lesion areas in addition to a low rCBF value of the whole brain.

SDS scores were independent of lesion size (SDS score: 46.4±14.3 for small lesion, 44.5±9.7 for medium lesion, 45.1±8.6 for large lesion), although rCBF value was low in patients with large brain lesion.

Relation Between Changes in SDS Score and Regional Cerebral Blood Flow
Table 3 shows the relation between change in SDS score and that in rCBF value during the follow-up period. All scalp sites showed significant inverse correlations between changes in SDS score and rCBF. Furthermore, higher inverse correlations were observed at specific regions in each hemisphere. These included the parietal and parieto-occipital regions in the right hemisphere and the anterior temporal and inferior frontal regions in the left hemisphere. Although these were comparable to regions where significant inverse correlations were obtained at the initial assessment, these correlation coeffi-
Table 2. Correlation Coefficient Between Regional Cerebral Blood Flow and SDS Score at Initial and Final Assessment

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Hemisphere</th>
<th>Channel</th>
<th>r</th>
<th>SD</th>
<th>r</th>
<th>SD</th>
<th>r</th>
<th>SD</th>
<th>Total SDS</th>
</tr>
</thead>
<tbody>
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<td>Initial</td>
<td>Right</td>
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<td>0.01</td>
<td>-0.23*</td>
<td>0.01</td>
<td>-0.15</td>
<td>0.01</td>
<td>-0.24*</td>
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<td></td>
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<td>54.5</td>
<td>12.7</td>
<td>57.5</td>
<td>15.2</td>
<td>47.1</td>
<td>11.6</td>
<td>63.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(17.7)</td>
<td>(17.2)</td>
<td>(16.6)</td>
<td>(17.1)</td>
<td>(15.8)</td>
<td>(14.5)</td>
<td>(14.9)</td>
</tr>
<tr>
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<td>Left</td>
<td>rCBF</td>
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<td>0.01</td>
<td>-0.22*</td>
<td>0.01</td>
<td>-0.17</td>
<td>0.01</td>
<td>-0.26†</td>
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<tr>
<td></td>
<td>SD</td>
<td></td>
<td>50.4</td>
<td>11.8</td>
<td>57.5</td>
<td>14.3</td>
<td>46.1</td>
<td>12.6</td>
<td>62.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(16.1)</td>
<td>(16.2)</td>
<td>(14.4)</td>
<td>(16.6)</td>
<td>(15.3)</td>
<td>(12.4)</td>
<td>(15.6)</td>
</tr>
<tr>
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<td>rCBF</td>
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<td>0.01</td>
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<td>0.01</td>
<td>-0.13</td>
<td>0.01</td>
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<td>54.0</td>
<td>12.7</td>
<td>58.2</td>
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<td>46.6</td>
<td>13.3</td>
<td>65.2</td>
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<td></td>
<td>(15.7)</td>
<td>(15.0)</td>
<td>(14.7)</td>
<td>(16.2)</td>
<td>(15.1)</td>
<td>(12.5)</td>
<td>(17.5)</td>
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<tr>
<td>Final</td>
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<td>rCBF</td>
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<td>0.01</td>
<td>-0.05</td>
<td>0.01</td>
<td>-0.20</td>
<td>0.01</td>
<td>-0.22*</td>
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<tr>
<td></td>
<td>SD</td>
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<td>50.6</td>
<td>11.8</td>
<td>60.0</td>
<td>14.3</td>
<td>46.3</td>
<td>13.3</td>
<td>63.6</td>
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<td></td>
<td>(14.0)</td>
<td>(15.5)</td>
<td>(13.3)</td>
<td>(16.6)</td>
<td>(15.3)</td>
<td>(10.9)</td>
<td>(17.7)</td>
</tr>
</tbody>
</table>

SDS, Zung Self-Rating Depression Scale; rCBF, regional blood flow.

*0.1>p>0.05; †p<0.05.

Discussion

The current longitudinal study demonstrated that improvement of test scores in poststroke depression was associated with an increase in rCBF. Although a significant correlation was observed on all scalp sites, specific cortical areas in each hemisphere were much more closely related to the change in mood state. Hypoperfusion in the right parieto-occipital region and in the left anterior temporal and inferior frontal regions accounted for more poststroke depression than other cortical areas. A significant inverse correlation between depression score and hemispheric rCBF value has already been reported in elderly normal volunteers and in patients with endogenous depression. The relation between changes in rCBF and mood state appears to be independent of recovery of physical impairment after stroke, because the SDS score was not related to neurological deficits after stroke. This is consistent with the finding that only 10% of the variance in depression scores was explained by physical impairment, whereas lesion location accounted for approximately 50% of the variance.

We did not obtain high correlations between rCBF and SDS score at the initial and final assessments, probably because absolute rCBF is likely to be influenced by factors such as age, gender, lesion location, extent of lesion, and poststroke duration. However, the fact that there were still some correlations between rCBF and SDS score at the two measurement times in some cortical regions suggests that regional brain function has a substantial influence on mood state after stroke. Additional longitudinal studies would help reduce effects of interindividual differences on the variability of rCBF value. The correlation between rCBF and SDS score at the final examination was low in...
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comparison with that of the initial examination. At the final examination, at least 1 year had passed since last stroke onset in all patients, whereas more than half of patients were within 1 year after stroke at the initial examination. The period in which lesion locations affect most strongly on poststroke depression was within 1 year after stroke. 20 Thus, final decreases in their correlations may be due to longer periods after stroke.

The current finding is consistent with the notion that poststroke depression is associated with regional cerebral dysfunction and that each hemisphere contributes differentially to depressive syndromes. Based on their analysis of lesion location, Robinson and his colleague 21 first demonstrated the significant contribution of left frontal damage to poststroke depression. They also found that lesions in the vicinity of the occipital pole in the right hemisphere increased the severity of depression. 4 Our rCBF data including the relation of lesion location and SDS score support their findings. Although significant association between SDS score and rCBF value does not necessarily imply causality, the data from lesion studies make it plausible that decreases of rCBF in certain brain areas contribute to depression. It was hypothesized that asymmetrical depletion in the cortical biogenic amine pathways due to lateralized brain damage plays a role in poststroke depression. 22 Another study showed a differential effect of each hemisphere on increased cortical S2-serotonin receptor binding activity after stroke. 23 The current study did not test the amine hypothesis directly but demonstrated a clear asymmet-

TABLE 3. Correlation Coefficient Between Changes in Regional Cerebral Blood Flow and SDS Score During Follow-up Period

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Channel</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>-0.37</td>
<td>-0.39</td>
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<td>-0.39</td>
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<td>-0.51</td>
<td>-0.30</td>
<td>-0.45</td>
<td>-0.46</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td>-0.29</td>
<td>-0.45</td>
<td>-0.37</td>
<td>-0.51</td>
<td>-0.52</td>
<td>-0.40</td>
<td>-0.41</td>
<td>-0.40</td>
<td>-0.40</td>
</tr>
</tbody>
</table>

SDS, Zung Self-Rating Depression Scale.
*p<0.01; †p<0.001; ‡p<0.05.
rical cortical contribution to poststroke depression. This may be related to the differential processing of emotional information in the human brain hemisphere.

A neural network involving the inferior frontal lobe, temporal pole, and subcortical limbic regions plays an important role in the regulation of mood in normal subjects, neurological patients, and primates. Hypometabolism in these regions was shown in patients with endogenous (primary) depression. Manic syndrome after brain injury was caused by hypometabolism in the right inferior temporal lobe, which was remote from the primary lesion. Thus, focal brain damage can cause an affective syndrome regardless of the primary or secondary effect of the lesion. Anatomic studies using CT or magnetic resonance imaging are not able to clarify whether a certain symptom results from the focal lesion per se or other remotely affected brain regions. In conjunction with the series of lesion data, the current study suggests that poststroke depression is exacerbated by the dysfunction of specific cortical areas probably related to the limbic system.

Another implication of the current study is a strategy for the treatment of poststroke depression. Tricyclic or tetracyclic antidepressants are widely recommended for the treatment of depression. These drugs also have been used for the therapy of poststroke depression. The current study suggests that poststroke depression could be treated with agents that improve microcirculation in the impaired brain tissue. Our laboratory has already started such trials and shown improvement of depression in association with increased rCBF.

The current study has several limitations. It should be pointed out that the criteria of patient selection could bias the sample composition. The current study excluded aphasic or demented patients who could be depressed. Furthermore, severely depressed patients to whom antidepressant medication had been given were also excluded to eliminate the effects of drugs on rCBF. The current study may also have included a methodological limitation in rCBF measurement. The spatial resolution of this method is not sufficient for assessing the rCBF value in small cortical areas. We also could not obtain CBF information from subcortical brain structures by this method. Subcortical neural structures such as the caudate nucleus have been reported to contribute to poststroke depression. Thus, the current study should be reexamined by more advanced methods such as positron-emission tomography, with simultaneous measurement of rCBF and metabolism within deep brain structures.

The current study shows that the affective disorders accompanying stroke bear no relation to the type or severity of the neurological deficits. The depressive features may improve or worsen in the absence of further strokes, as judged by both clinical and neuroimaging features. Regional perfusion in certain regions of both hemispheres consistently vary inversely with the affective status (particularly left frontotemporal and right parieto-occipital regions). This implies a reversible pathogenesis that is influenced by changes in cerebral perfusion and, therefore, may be amenable to treatment.

Acknowledgments

We would like to thank Kazuya Yamashita, M.D.; Hitoshi Fukuda, M.D.; Hirokazu Bokura, M.D.; Nobuo Suyama, M.D.; and staffs at the Institute of Shimane Health Science for assistance in this project.
Bar graphs show regional cerebral blood flow (rCBF) change in the patient group with worsened Zung Self-Rating Depression Scale score. Significant reductions in rCBF were noted at the parietal and parieto-occipital regions in the right hemisphere and the inferior frontal and anterior temporal regions in the left hemisphere.
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