Regional Cerebral Blood Flow in Stroke:
Hemispheric Effects of Cognitive Activity

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Regional cerebral blood flow (rCBF) was measured with the xenon-133 inhalation technique in 15 patients with unilateral cerebral infarction and 12 matched controls. Measurements were performed during a standard resting baseline condition and during the performance of standardized verbal analogies and spatial line orientation tasks. Resting and activated CBF were lower in patients than in controls, and there were differences in the hemispheric pattern of activated CBF. Control subjects replicated earlier findings of asymmetric increase in CBF for the cognitive tasks, whereas patients showed abnormalities in lateralized CBF changes consistent with side of infarction. These findings underscore the utility of cognitive challenges in the study of rCBF in stroke. This can lead to an experimental paradigm in clinical studies of the relation between behavioral deficits and regional brain dysfunction and may also improve the utility of CBF measurements in clinical settings. (Stroke 1987;18:776-780)

The xenon-133 inhalation technique provides a noninvasive method for determining regional cerebral blood flow (rCBF). It has been applied extensively in the study of the effects of stroke. Previous reports have documented overall reduction in rCBF, but data on the effects of unilateral cerebral infarction (CI) on hemispheric rCBF have been inconsistent. The measurement of hemispheric rCBF changes during cognitive activity in relation to the side of anatomic lesions may help us understand the behavioral consequences of stroke and its effects on physiologic changes in regional brain function.

Most studies of rCBF in CI performed thus far are of limited value for addressing this relation because the rCBF measurements were obtained during resting conditions. The exceptions are the studies of Meyer et al. and Knopman et al. Meyer et al studied rCBF in 14 patients with left hemispheric ischemic infarction and aphasia, 6 with severe infarctions and poor recovery from aphasia and 8 with mild-to-moderate infarctions and good recovery. They used multimodal stimulation and for the first group reported bilaterally reduced hemispheric CBF during stimulation, with reduction in left hemispheric rCBF in Broca's and Wernicke's areas. In the mild group there was bilateral increase in CBF, with right hemisphere blood flow greater than left. The data were interpreted as supporting the transfer of language functions to the right hemisphere in association with recovery. Knopman et al measured rCBF in 21 aphasic patients with left hemispheric ischemic infarction at resting baseline and during an auditory verbal comprehension task. They reported increased right hemispheric CBF associated with recovery from aphasia, supporting the hypothesis that such recovery coincides with increased right hemispheric involvement in language comprehension. The behavioral deficits in CI presumably reflect failure of brain regions to be activated in response to task demands. These findings encourage a more systematic examination of the relation between hemispheric changes in CBF and cognitive activity.

There is evidence that cognitive tasks produce systematic changes in hemispheric rCBF. Gur et al reported that, in normal subjects, performance of a verbal analogies task produced a greater increase in left-hemispheric CBF, whereas right-hemispheric CBF increased more for a spatial task requiring judgment of line orientation. We report the results of applying the same tasks to a sample of patients with unilateral CI.

Subjects and Methods

Subjects

Fifteen patients were selected from consecutive admissions and outpatient visits at the neurology services of the Hospital of the University of Pennsylvania and The Graduate Hospital. A laterality questionnaire was administered to exclude left-handed patients. Only patients with a completed CI as evidenced by a clear unilateral deficit that lasted > 24 hours were admitted to the protocol. A computed tomography (CT) scan was performed on admission to the hospital. In addition, an echocardiogram and Doppler studies of the carotid arteries were used to exclude major vaso-


Supported by National Institutes of Health Grant NS 19039, National Institute of Health Grant MH 30456, and The Spencer Foundation. F.L.S. was supported by the Ontario Heart Foundation.

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Received November 17, 1986; accepted February 16, 1987.
lar disease and diagnoses other than ischemic, non-hemorrhagic CI. All patients were neurologically stable at the time of study, and their deficit was sufficiently mild to permit participation. All were treated with aspirin, and 4 patients, studied within 3 days after infarction, received no other medications. The 11 other patients were treated with antihypertensive medication.

On the basis of the clinical data, patients were assigned to one of two groups: left-hemispheric cerebral infarction (LCI) \((n = 8)\) and right-hemispheric cerebral infarction (RCI) \((n = 7)\). Diagnostic assignment was performed independently by two neurologists with complete agreement. Pertinent characteristics of the sample are summarized in Table 1.

The controls \((C) (n = 12)\) were right-handed, identically screened, and were balanced with patients for sex ratio (male:female, LCI 5:3; RCI 5:2; C 5:7) and age (mean ± SD, LCI 63.6 ± 8.9; RCI 51.9 ± 9.3; C 56.1 ± 11.8 years) \([F(2,24) = 2.48, \text{not significant}]\). The 3 groups did not differ in hemoglobin levels (LCI 14.0 ± 1.6; RCI 14.7 ± 1.3; C 14.4 ± 1.6 mg/100 ml) \([F(2,24) < 1]\), systolic (LCI 133.3 ± 18.8; RCI 137.0 ± 19.4; C 132.5 ± 10.0 mm Hg) \([F(2,24) < 1]\) and diastolic blood pressure (LCI 81.6 ± 15.4; RCI 85.0 ± 6.5; C 81.6 ± 6.6) \([F(2,24) < 1]\). The 2 patient groups did not differ in time since ictus (LCI 38.1 ± 55.7; RCI 43.3 ± 72.3 days) \((t_{13} < 1)\).

**Procedures**

The purpose and procedures were explained to the subjects in detail, and informed consent was obtained. A complete history was obtained and neurologic examination performed immediately before the rCBF study.

Three rCBF determinations (during resting baseline and verbal analogies and spatial line orientation tests) were made on each subject in a single session. The measurements were separated by at least 15 minutes to assure that background activity was at acceptable levels (< 10% of peak counts). The verbal analogies were adapted from the Scholastic Aptitude Test with the 4 response pairs presented underneath the test analogy pair. The spatial task was an adaptation of the Benton Line Orientation Test. Subjects were shown pairs of lines that varied in length and orientation and were asked to indicate, on an array presented below the stimulus field, the lines corresponding to the stimulus. Five practice trials were provided for each task, and subjects proceeded at their own pace. Tasks were initiated 5 minutes before inhalation of xenon-133 and continued throughout the 15 minutes of uptake and clearance measurement, for a total of 20 minutes.

Order of conditions was randomized across subjects in a Latin square design. Ambient noise and lighting were kept to the minimum required for operation of the laboratory. Subjects had their eyes open in all conditions, and their ears were not occluded. Subjects were in a supine position, and test stimuli were projected on an overhead screen. Response modes in the 2 tasks were equated by having subjects indicate their response with a flashlight held in both hands. Patients with hemiparesis could still hold the flashlight with both hands.

<table>
<thead>
<tr>
<th>Patient/Age/Sex</th>
<th>Interval from ictus, days</th>
<th>Neurologic deficit at time of study</th>
<th>CT scan findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left hemispheric infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/66/M 8</td>
<td>None</td>
<td>L parietal infarct</td>
<td></td>
</tr>
<tr>
<td>2/71/F 2</td>
<td>R arm weakness</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>3/79/M 10</td>
<td>R hemiparesis</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>4/63/F 8</td>
<td>R hemiparesis, R homonomous hemianopia</td>
<td>L parietal, L occipital infarct</td>
<td></td>
</tr>
<tr>
<td>5/60/F 150</td>
<td>R hemiparesis</td>
<td>L frontal infarct</td>
<td></td>
</tr>
<tr>
<td>6/64/F 2</td>
<td>Anomic aphasia</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>7/56/M 100</td>
<td>Broca’s aphasia</td>
<td>L frontal infarct</td>
<td></td>
</tr>
<tr>
<td>8/50/M 25</td>
<td>R hemiparesis</td>
<td>L internal capsule</td>
<td></td>
</tr>
<tr>
<td><strong>Right hemispheric infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/53/M 19</td>
<td>None</td>
<td>R frontal infarct</td>
<td></td>
</tr>
<tr>
<td>2/60/M 10</td>
<td>L leg weakness</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>3/55/M 201</td>
<td>L hemiparesis</td>
<td>R frontal infarct</td>
<td></td>
</tr>
<tr>
<td>4/40/M 59</td>
<td>L hemiparesis</td>
<td>R frontal infarct</td>
<td></td>
</tr>
<tr>
<td>5/64/F 2</td>
<td>L hemiparesis</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>6/41/M 9</td>
<td>L hemiplegia</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>7/50/F 3</td>
<td>L hemiparesis</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

The patients with no neurologic deficit at the time of study had hemiparesis that cleared; CT scans were obtained within 48 hours of admission. L, left; R, right; CT, computed tomography.
CBF was determined by the xenon-133 inhalation technique. Trace amounts of $^{133}$Xe (5–7 mCi/l) in air were inhaled through a face mask for approximately 60 seconds. The uptake and clearance of the isotope from the brain were monitored by 16 collimated sodium iodide crystal detectors placed over the scalp (Figure 1). rCBF was computed from the clearance rates, as described by Obrist and Wilkinson. The clearance curves were analyzed for 14 minutes after inhalation. The 14-minute analyses were preferred over shorter intervals because they increase the stability of the computed parameters. The integrity of the rCBF measurements was evaluated for absence of artifacts, good count rates and curve fits, and adequate estimation of end-tidal carbon dioxide levels. There were no differences in carbon dioxide levels measured with a capnograph in mm Hg between LCI patients (mean ± SD, resting 35.6 ± 2.6; verbal 35.2 ± 2.3; spatial 34.9 ± 5.4), RCI patients (resting 36.4 ± 3.6; verbal 35.7 ± 3.4; spatial 35.6 ± 3.2), and controls (resting 36.4 ± 3.4; verbal 36.1 ± 3.1; spatial 35.8 ± 3.2) [all $F(2,24) < 1$]. The rCBF values for the 2 activation measurements in each subject were corrected to the resting baseline carbon dioxide level. The correction factor was 3%/mm Hg change in Pco2. The statistical analyses were also performed on the uncorrected data, and the effects reported here persisted.

Results

The dependent variable was IS of Obrist and Wilkinson, which is an index of flow defined as the tangent at time zero for an equivalent bolus injection. IS is more sensitive than Risberg’s ISI to blood flow in the fast-clearing, gray matter compartment. IS was preferred over the traditional measure of gray matter flow, F1, because it is more stable in pathologic conditions. Analyses were also performed for F1 and CBF-15, the mean flow of the fast and slow compartments, with similar results.

Table 2 presents the hemispheric means for each measure across groups and conditions. The results were analyzed with an analysis of variance (ANOVA) procedure using diagnosis as a grouping factor (LCI, RCI, C) and task (resting, verbal, spatial) and hemisphere (left, right) as within-group factors. There was a significant effect of task [$F(2,48) = 14.62, p < 0.0001$], indicating higher CBF during cognitive activity compared with resting. A task × hemisphere interaction [$F(2,48) = 3.28, p = 0.046$] indicated that across all groups there was a relatively greater increase in the left hemisphere CBF for the verbal task and a greater right hemisphere increase for the spatial task. This effect, however, was different in the patient and control groups as indicated by the hypothesized higher-order task × hemisphere × diagnosis interaction [$F(4,48) = 3.03, p = 0.026$]. This interaction is illustrated in Figure 2.

To evaluate which specific differences are significantly responsible for the higher-order interaction, the three-way interaction was decomposed using the simple-effects procedure of Davidson and Toporek for univariate contrasts. The controls duplicated the pattern seen in our studies with younger normal subjects, with higher left hemispheric CBF for the verbal relative to higher right hemispheric CBF for the spatial task ($p = 0.011$). This pattern was not significant for either group of patients. LCI patients showed no overall activation for the verbal task and only a marginally significant overall increase for the spatial task ($p = 0.051$, one-tailed). There were no significant effects of task on hemispheric CBF asymmetries. By contrast, RCI patients showed significant overall activation for both the verbal ($p = 0.016$) and spatial tasks ($p = 0.030$). Furthermore, they had greater left than right hemispheric activation for both the verbal ($p = 0.031$) and spatial tasks ($p = 0.017$).

Additional univariate analyses were performed to compare patients (LCI and RCI combined) with controls for each task condition. For resting baseline, patients had significantly lower flows than controls ($p = 0.031$). When each subgroup of patients was compared with controls, there was a marginally significant reduction in overall CBF for LCI ($p = 0.07$, one-tailed) and a significant reduction for RCI ($p = 0.033$, one-tailed). For the verbal task, patients had lower overall flows than controls ($p = 0.028$). Subgroup comparisons showed that the LCI group had lower CBF than controls ($p = 0.043$), whereas the RCI group did not differ from controls. For the spatial task as well, patients had lower flows ($p = 0.009$), and each group separately had lower CBF (LCI, $p = 0.026$; RCI, $p = 0.048$). Thus, RCI patients were most clearly differentiated from controls during the spatial task, whereas LCI patients were differentiated from controls during both tasks.

To evaluate task performance, the proportion of correct responses for the verbal and spatial tasks administered during the rCBF session were calculated. Standard (z-score) transformations of those proportions were the dependent measure in a diagnosis × task ANOVA. There was a significant effect of diagnosis [$F(2,24) = 5.25, p = 0.014$], indicating that controls performed better than patients. No other effects or interactions were significant. The task × diagnosis interaction was not significant, probably because of the mild impairment of these subjects and the small sample size considering the power of the statistical tests.

![Figure 1. Schematic probe configuration, intended to cover the middle cerebral artery distribution.](image-url)
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Also consistent with these earlier studies, congruent with hemispheric specialization of function, during cognitive activity, with laterality of changes in blood flow increases.  

In contrast to controls, patients with hemispheric infarcts demonstrated abnormalities in the laterality of cerebral blood flow. RCI patients showed greater disturbance in right hemispheric activation for the spatial task, whereas LCI patients showed greater left hemispheric impairment of activation for the verbal task. The results for LCI are consistent with the data of Meyer et al on a similar group of patients with mild-to-moderate infarcts. The comparison with the RCI group suggested further evidence that hemispheric infarction disturbs the normal pattern of lateralized cerebral activation in accordance with task demands. This supports the notion that behavioral deficits associated with CI may reflect failure of brain regions to become active in response to cognitive challenges.

The side of a stroke also affected the magnitude of asymmetry of hemispheric CBF increase produced by cognitive activation (Figure 2). RCI patients had a normal activation pattern for the verbal task (increased left hemispheric activation) and relative bilateral reduction in overall activation for the spatial task. LCI patients showed reduced activation for both tasks. In view of the lack of an hypothesis that the side of a lesion is related to the degree of cortical activation impairment during cognition, replication of this study is indicated.

The effects obtained may be metabolic or hemodynamic. Specifically, the reduced augmentation of CBF during cognition can be a primary defect of tissue metabolism associated with ischemic neuronal damage. It could also be attributed to a hemodynamically compromised cerebral circulation unable to respond to the increased metabolic demands of cognitive activation. In the intact brain neural activity, cerebral metabolism and blood flow are tightly coupled. CI is associated with neuronal loss and concomitant decrease in metabolism and blood flow. Abnormalities in blood flow changes during cognitive activation may reflect failure of brain regions to become metabolically activated. On the other hand, it is possible that vascular disease impairs the capacity for an appropriate increase in perfusion during cognitive activity. This question can be addressed by assessing the relation between individual patterns of CBF changes in patients who differ in the degree of clinical impairment, the amount of neural loss, and the extent of vascular disease. The question can also be answered by

**Table 2. IS, F1, and CBF-15 in Controls and Patients With Left and Right Cerebral Infarct**

<table>
<thead>
<tr>
<th>Group</th>
<th>LH IS</th>
<th>RH IS</th>
<th>LH F1</th>
<th>RH F1</th>
<th>LH CBF-15</th>
<th>RH CBF-15</th>
<th>LH Spatial</th>
<th>RH Spatial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>62.43 ± 8.64</td>
<td>63.26 ± 8.69</td>
<td>65.60 ± 5.54</td>
<td>66.23 ± 5.50</td>
<td>41.02 ± 7.54</td>
<td>41.47 ± 8.09</td>
<td>63.05 ± 6.62</td>
<td>63.26 ± 8.69</td>
</tr>
<tr>
<td>LCI</td>
<td>53.10 ± 4.85</td>
<td>53.70 ± 5.34</td>
<td>59.26 ± 6.74</td>
<td>59.81 ± 6.30</td>
<td>37.55 ± 5.19</td>
<td>37.90 ± 5.79</td>
<td>51.06 ± 11.25</td>
<td>50.05 ± 13.01</td>
</tr>
<tr>
<td>RCI</td>
<td>51.83 ± 5.12</td>
<td>50.05 ± 13.01</td>
<td>59.38 ± 14.38</td>
<td>57.35 ± 10.77</td>
<td>36.59 ± 8.07</td>
<td>35.74 ± 7.57</td>
<td>51.06 ± 11.25</td>
<td>50.05 ± 13.01</td>
</tr>
</tbody>
</table>

IS, initial slope of impulse equivalent clearance curve; F1, fast-flow compartment (ml/100 g/min); CBF-15, mean flow of fast and slow compartments (ml/100 g/min); LH, left hemisphere; RH, right hemisphere; CI, cerebral infarct. Values are mean ± SD.

**Discussion**

The results for controls are consistent with our previous studies with normal subjects and with reports from other laboratories indicating increased CBF during cognitive activity, with laterality of changes congruent with hemispheric specialization of function. Also consistent with these earlier studies, these effects are small and superimposed on a bilateral increase in CBF. The reliable hemispheric effects were attributed to the consistency of asymmetry rather than the magnitude.

In contrast to controls, patients with hemispheric infarcts demonstrated abnormalities in the laterality of CBF increase. RCI patients showed greater disturbance in right hemispheric activation for the spatial task, whereas LCI patients showed greater left hemispheric impairment of activation for the verbal task. The results for LCI are consistent with the data of Meyer et al on a similar group of patients with mild-to-moderate infarcts. The comparison with the RCI group suggested further evidence that hemispheric infarction disturbs the normal pattern of lateralized cerebral activation in accordance with task demands. This supports the notion that behavioral deficits associated with CI may reflect failure of brain regions to become active in response to cognitive challenges.

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![Figure 2. Hemispheric cerebral blood flow for resting (R), verbal (V) and spatial (S) conditions in patients and matched controls.](http://stroke.ahajournals.org/)

**Figure 2. Hemispheric cerebral blood flow for resting (R), verbal (V) and spatial (S) conditions in patients and matched controls.**
future positron emission tomography studies in which glucose and oxygen metabolism are compared with CBF in the same individuals.

The hemispheric asymmetries of changes in CBF have been attributed to the effects of cognitive activity. This seems justified because the stimulation and response modalities were equal for the verbal and spatial tasks with respect to sensorimotor and attentional components, and only patients who could manipulate the flashlight and perform the cognitive tasks were studied. However, the sensorimotor and attentional components merit more specific investigation to identify their contribution to CBF changes in normal and pathologic conditions.

The results of the present investigation should be regarded as preliminary in view of the small and heterogeneous sample. However, they suggest a potential use of the cognitive activation paradigm in a systematic study of brain–behavior relations. In this initial step, only hemispheric effects were examined. Future research can use tasks aimed at activating more specific regions and relate behavioral deficits to abnormalities in blood flow changes for appropriate brain regions. Larger and more homogeneous populations will be needed for such studies, and follow-up data will be necessary to establish the relation between activation patterns and recovery. The potential of cognitive challenge procedures for improving the clinical utility of the 133Xe technique also merits further investigation to determine whether these group effects are helpful in identifying cerebral disease in individual patients. It also remains to be seen whether abnormalities in rCBF changes during cognitive activity predict recovery, as suggested by Knopman et al., and whether the pattern of abnormality may assist in identification of patients who are at higher risk for further ischemic events.

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Key Words • rCBF • xenon-133 inhalation technique • cognitive activation • unilateral cerebral infarct • verbal and spatial tasks
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Stroke. 1987;18:776-780
doi: 10.1161/01.STR.18.4.776

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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