Remote Cortical Dysfunction in Aphasic Stroke Patients

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We studied the effect of deep-seated left hemispheric lesions on cortical blood flow in 18 right-handed aphasic stroke patients. Regional cerebral blood flow was measured at rest and during the performance of a functional naming test using the two-dimensional xenon-133 inhalation method. Compared with 10 controls, at rest the patients showed regional cortical hypoperfusion in the left frontoparietal region. In the controls, activation patterns from the rest to the test condition involved mainly the left hemisphere areas. In the patients, a lack of blood flow change was observed in several areas that were usually hypoperfused at rest. However, in patients with slight verbal expression disorders there were obvious blood flow increases in other brain regions in both hemispheres. Such cortical functional reorganization and the presence of a remote cortical dysfunction could play a role in the pathophysiology of language disorders.

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Various studies using different methods have demonstrated reductions of blood flow or metabolism in structurally intact brain areas. Such reductions occur in the cerebral hemispheres both contralateral1-6 and ipsilateral1-5,19 to the lesion and in the cerebellum contralateral to a supratentorial lesion.20-28 This phenomenon in areas remote from the lesion could represent the hemodynamic or metabolic concomitant of the depression of neuronal activity called “diaschisis” described by von Monakow in 1914.29

How behavior can be altered by such distant effects is still a matter of discussion. In crossed cerebellar diaschisis cerebellar signs are generally missing, but in cases with deep-seated hemispheric lesions it has been suggested that cortical diaschisis could contribute to the clinical picture.10-18 However, most observations are restricted to a description of clinical signs that cannot be fully explained by the localization of the morphological lesion on computed tomography (CT) and of regional reduction in cortical blood flow or metabolism. Nevertheless, among patients with deep-seated left hemispheric lesions, Skinhej Olsen et al.13 observed cortical blood flow decreases only in aphasic cases. Metter et al.10 observed that cortical metabolism was reduced only moderately in patients with slight language disorders. We also reported earlier that the localization of the cortical reduction in regional cerebral blood flow (rCBF) was different in nonaphasic and aphasic cases and that the phenomenon was more important when language disorders were severe.16 In all these studies, however, remote reduction in rCBF or metabolism was observed only in patients studied at rest. To assume that such decreased cortical activity may give rise to clinical signs, the cortical dysfunction should persist during the performance of functional tests for which the activation of involved regions is necessary in normal subjects. We therefore studied brain activation patterns in aphasic stroke patients whose morphological lesions on CT were deep-seated and spared the cortex.

Subjects and Methods

We studied 18 right-handed aphasic stroke patients ranging in age from 45 to 84 years (10 men and eight women, mean age 66 years). A control group of 10 normal subjects (four men and six women, mean age 36 years) was also studied. All stroke patients had been admitted to our department for speech therapy and had undergone a complete neurological investigation. We assessed hand preference by using the Edinburgh Inventory30 and language by using a series of classical tests currently used in our department31,32 and covering various aspects of oral and written language. Verbal comprehension was slightly disturbed in most patients, whereas the severity of verbal expression disorders assessed by a quantitative index Ie (range: 0, severely disturbed to 100, normal)33 varied from patient to patient. On the basis of the Ie values, we divided our patient population into two subgroups: severely affected patients (Ie of <50,
FIGURE 1. Regional cerebral blood flow (rCBF) landscape at rest in right (R) and left (L) hemispheres of a: normal subjects (n=10), b: aphasic patients (n=18), c: slightly affected patients (n=12), and d: severely affected patients (n=6). Small numerals indicate conventional numbering of detectors. Deviations from mean hemispheric values are represented as clock symbols. Relative to vertical (12 o'clock) position, clockwise deviation indicates rCBF value greater than mean hemispheric value and counterclockwise deviation indicates rCBF value less than mean hemispheric value (90° corresponds to 15% deviation). *p<0.002 different from normal subjects by Student's unpaired t test.

n=6, mean age 65 years) and slightly affected patients (Ie of >50, n=12, mean age 67 years). In all patients, CT was performed between the 15th and 30th day after stroke onset and revealed a single, deep-seated left hemisphere vascular lesion that spared the cortex even at the depth of the sulci. We excluded lacunes.

We measured rCBF using the two-dimensional xenon-133 inhalation method. The holding blocks carried 32 head detectors (¾×¾-in. NaI Tl scintillation crystals) with cylindrical lead collimators. The subject's head was carefully positioned, and the detectors were placed in parallel planes making an 11° angle with the canthomeatal line (the conventional numbering of the 32 detectors is presented in Figure 1). The rCBF values were expressed as the initial slope index (ISI) calculated between 30 and 90 seconds after the beginning of the xenon washout. The carbon dioxide concentration in the expired air was recorded by a capnograph, and the rCBF results were corrected for PCCO2 according to Maximilian et al (i.e., 0.75 ISI units for each millimeter of mercury deviation from 40 mm Hg). Because ISI is dominated by the cortical gray matter blood flow, only cortical rCBF values were effectively measured. All subjects were instructed about the task before beginning and were fully cooperative. The first measurement was taken at rest with the subject lying in a quiet room with eyes open and ears unplugged. Thirty minutes later with the head position unchanged, a second rCBF measurement was taken during a functional task: the subject was asked to name familiar objects (ball, battery, screw, knife, etc.) held out by hand in succession at 5-second intervals during the washout
period. All patients performed verbally during the second rCBF-measuring session although the quality of performance was variable because of various language disorders. The order of measurements was not counterbalanced. We are not in a position to quantify possible anxiety linked to the test, but the subjects were interrogated after the recordings and never complained of any notable distress.

Clinical evaluation and rCBF measurements were performed 1 month (30±9 days) after the stroke. To compare regional blood flow values at rest between the controls and the patients, rCBF values were expressed as a percentage of the hemispheric mean. Statistical analysis was achieved by using unpaired t tests (because multiple comparisons were performed, stringent significance levels were assigned). The significance of rCBF changes between the rest and test conditions was assessed in each group by analysis of variance (ANOVA) followed by Bonferroni t tests.

Results
In the controls, mean hemispheric blood flow values at rest were 64.2±9.0 on the right and 63.6±8.9 on the left. In the patients, these values were lower, namely, 43.3±6.8 on the right and 40.2±7.0 on the left (t=6.94, p<0.001 and t=7.69, p<0.001, respectively). When the aphasic population was divided into subgroups of slightly and severely affected patients, these values were 43.7±5.3 and 42.4±9.0 on the right and 41.1±5.1 and 38.4±9.5 on the left, respectively. These values did not differ significantly.

Because the degree of blood flow decrease was not the same in all regions, rCBF values were also expressed as a percentage of the hemispheric mean value. Compared with the controls, the patients showed left hemisphere regional cortical hypoperfusion mainly in the prerolandic areas. This hypoperfused zone was more extensive in the severely affected patients. We observed relative hyperperfusion in some areas of the right hemisphere as a result of blood flow redistribution (Figure 1).

In the controls, mean hemispheric blood flow values did not change significantly on the right (6.1% increase) during the functional test whereas a significant increase of 10.5% was observed on the left (t=3.36, p=0.008). The results of repeated-measures ANOVA were significant in both hemispheres (F=2.69, p=0.001 on the right and F=2.75, p<0.001 on the left). Significant rCBF changes from the rest to the test condition were observed mainly in the left hemisphere, in the frontotemporal region (detectors 20 and 22) including Broca's area, in the parietotemporo-occipital junction (Figure 2).

In the patients, mean hemispheric blood flow values increased significantly during the functional test on both sides (on the right 9.0%, t=3.07, p=0.007 and on the left 10.7%, t=2.65, p=0.017). However, these changes were significant only in the subgroup of slightly affected patients (on the right 11.0% increase, t=2.95, p=0.013 and on the left 11.9% increase, t=2.24, p=0.047). Mean hemispheric blood flow values did not change significantly in the subgroup of severely affected patients (on the right 5.4% increase and on the left 8.1% increase).

In the population of aphasic patients as a whole, significant rCBF changes from the rest to the test condition were observed in both hemispheres (by repeated-measures ANOVA F=2.16, p=0.007 on the right and F=2.87, p<0.001 on the left); rCBF increased significantly at the parietotemporo-occipital junction, in the parietal and occipital areas bilaterally, and in the right temporal area. We observed no significant rCBF change in these patients in several areas that were activated in the controls, namely, the frontal region (detectors 20 and 21, which were hypoperfused at rest) and in the frontotemporal region (detector 22) (Figure 2).

Significant rCBF changes between the rest and test conditions were observed in both subgroups of patients. In the slightly affected patients, results of repeated-measures ANOVA were F=2.17, p=0.008 on the right and F=2.54, p=0.001 on the left; in the severely affected patients, results were F=2.18, p=0.012 on the right and F=1.77, p=0.05 on the left. The rCBF increases involved more areas in the former subgroup than in the latter in both hemispheres. No significant rCBF change was ever observed in the frontal region (detectors 20 and 21, which were hypoperfused at rest) or in the frontotemporal region (detector 22) in either subgroup. In the subgroup of severely affected patients, a significant rCBF increase was observed in an area that was hypoperfused at rest (detector 27) (Figure 2).

Discussion
The 133Xe inhalation method used in this study has limitations but is suitable for performing several measurements in the same patient. We measured rCBF after the same poststroke interval because in stroke patients activation patterns during the performance of a functional task may change over time.

In the patients, mean hemispheric blood flow values at rest were lower than in the controls. Such observations are usual in stroke patients and are ascribed mainly to advancing age and the presence of risk factors for atherothrombotic stroke. It is therefore not surprising that mean hemispheric blood flow values did not differ in our subgroups of severely and slightly affected patients since mean ages were similar in the two subgroups.

The only morphological lesions demonstrated by CT in our patients were confined to deep regions beyond even the sulci of the cortex. Therefore, the cortical rCBF decreases observed in several left hemisphere areas should correspond to a remote decrease in neuronal activity.

It is worth noting that, in our experience with the two-dimensional 133Xe inhalation technique, no sig-
Several rCBF changes in the parieto-occipital and occipital areas (detectors 15, 31, and 32) were present in all subjects (controls and patients) and could be related to the visual component of the functional task. Activation in the right frontal and temporal areas (detectors 6, 9, and 10), present only in the slightly affected patients, could reflect a partial shift of language to the right side. Such a transfer has already been suggested by clinical and rCBF studies, dichotic listening tests, amobarbital sodium tests, and evoked potentials. In our aphasic patients, no significant rCBF increase was observed in the left frontal and frontotemporal areas (detectors 20, 21, and 22). Among these areas, two were considered to be hypoperfused at rest. The lack of rCBF changes from the rest to the test condition in areas that were activated in the controls (including regions already hypoperfused at rest) suggests that such areas are functionally disconnected. This lack of activation during the performance of a functional...
task seems to be more consistent with the concept of diaschisis than observations made at rest and could explain the occurrence of aphasia. The presence of extensive activation patterns in both hemispheres in the slightly affected patients suggests that language disorders remain mild when cortical reorganization is possible. Thus, remote cortical dysfunction and cortical functional reorganization could both play a role in the pathophysiology of the clinical picture.

As far as the pathophysiology of clinical recovery is concerned, release from diaschisis is one of the mechanisms classically invoked. Our study was specific and was performed at approximately 1 month after the stroke. Changes in remote cortical effects might occur later, but we have no data to suggest this at present. In further studies, rCBF or metabolism recordings should not be restricted to measurements performed at rest.

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