Left Hypofrontality Correlates with Blunted Affect in Schizophrenia

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Abstract: Regional cerebral blood flow (rCBF) during the resting state was measured using the $^{133}$Xe inhalation technique in 39 patients diagnosed as having schizophrenic disorder according to the DSM-III criteria and 30 age- and sex-matched healthy volunteers. All the patients were receiving neuroleptic medication. The bilateral hemispheric mean flow values in the schizophrenic patients decreased significantly and the relative flow distribution reduced significantly only in the left frontal region compared to the controls. The lower the left frontal blood flow in schizophrenics, the more pronounced were the negative symptoms including blunted affect, avolition-apathy and inattention. These results suggest that the negative symptoms in schizophrenics are related to left frontal lobe dysfunction.

Key Words: regional cerebral blood flow, $^{133}$Xe inhalation technique, left hypofrontality, negative symptoms, schizophrenia


INTRODUCTION

After Ingvar and Franzén first demonstrated the abnormal distribution of cerebral blood flow in schizophrenic patients,9,10 “hypofrontality” in schizophrenics has been repeatedly reported in the regional cerebral blood flow (rCBF) and regional brain metabolism studies.4,6 In our previous study,11 we also confirmed the reduced frontal blood flow in patients with schizophrenia. Only a few reports,12,16,18 however, have studied the correlation between the clinical symptoms and rCBF.

SUBJECTS AND METHODS

Subjects

Thirty-nine medicated patients (26 men and 13 women) who gave informed consent to participate in this study were selected from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Kanazawa University Hospital. The patients fulfilled the DSM-III criteria for schizophrenic disorder. Their mean age was $27.3 \pm 5.5$ (SD) and the mean duration of the illness was 5.8 years.
The Wechsler Adult Intelligence Scale (WAIS) was completed on each patient and only patients with a full IQ above 70 were included.

The control sample consisted of 30 normal volunteers (20 men and 10 women) with a mean age of 28.0±5.2. There were no significant differences in age, sex, or handedness between the patients and controls.

**rCBF Measurements**

rCBF was measured by means of the $^{133}$Xe inhalation technique (Meditronic-Novo Diagnostic System, Inhalation Cerebrograph, Denmark). The device was equipped with 16 scintillation detectors on each hemisphere, but we used the values of only six detectors on each hemisphere to avoid artifacts. These six were on the frontal, frontocentral, temporal, centroparietal, temporoparietal and parietal regions. The location of the detectors is shown in Fig. 1. The measurements were carried out in a quiet, semi-darkened room with the subjects at rest and eyes closed. We excluded the patients whose respiration rates were irregular or too slow, or who showed apparent drowsiness in simultaneously monitored EEG. The values for rCBF were computed using the initial slope index (ISI) with the revised Fourier analysis.

**Clinical and Neuropsychological Assessments**

The clinical symptoms were assessed by two psychiatrists using the Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS), and each mean score was adopted. The patients were also given the WAIS, Wechsler Memory Scale, Benton Visual Retention Test and Wisconsin Card Sorting Test.

**CT Measurements**

CT scans were obtained from 22 schizophrenic patients (13 men and 9 women, mean age; 27.2±5.7) using an EMI head scanner with a slice thickness of 10 mm. We measured with a planimeter the area of the third ventricle, bilateral sylvian fissures, bilateral lateral ventricles and anterior cerebral fissure, and expressed these as a percentage of the area of the inner table of the skull in the same slice.

**Statistical Analysis**

The differences in rCBF between the schizophrenic and control groups were examined by the Student's t-test, with the statistical significance defined as $p<0.05$. The correlation analyses were done using Spearman's rank correlation coefficients and the statistical significance was taken as $p<0.01$ for a multiple comparison.

**RESULTS**

The mean hemispheric values of rCBF and the regional distribution values (percentage of hemispheric mean), as well as the absolute values of rCBF, were studied.

Table 1 shows the results of rCBF measures in the patient and control groups. The mean blood flow of both hemispheres was significantly reduced in the schizophrenic patients compared to the controls. The absolute values of rCBF in each region were also significantly decreased, especially in the left frontal region. The regional distribution value was, however, significantly lower only in the left frontal region in the schizophrenics as
Left Hypofrontality in Schizophrenia

Table 1: Comparison between Controls and Schizophrenics on Absolute Flow Values (ISI) and Regional Distribution Values

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 30)</th>
<th>Schizophrenics (N = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISI (ml/100 g/min)</td>
<td>Regional Distribution Value (%)</td>
</tr>
<tr>
<td><strong>Left hemisphere</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal (F)</td>
<td>56.2±8.1</td>
<td>106.0±5.2</td>
</tr>
<tr>
<td>Frontocentral (FC)</td>
<td>54.3±7.7</td>
<td>102.2±4.2</td>
</tr>
<tr>
<td>Temporal (T)</td>
<td>53.8±8.0</td>
<td>101.3±3.6</td>
</tr>
<tr>
<td>Centroparietal (CP)</td>
<td>52.5±7.2</td>
<td>98.9±3.6</td>
</tr>
<tr>
<td>Temporoparietal (TP)</td>
<td>51.9±7.6</td>
<td>97.8±3.9</td>
</tr>
<tr>
<td>Parietal (P)</td>
<td>49.9±7.8</td>
<td>93.8±3.8</td>
</tr>
<tr>
<td>Hemispheric mean</td>
<td>53.1±7.4</td>
<td>—</td>
</tr>
<tr>
<td><strong>Right hemisphere</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal (F)</td>
<td>56.3±7.7</td>
<td>104.4±4.8</td>
</tr>
<tr>
<td>Frontocentral (FC)</td>
<td>55.0±7.3</td>
<td>102.0±3.9</td>
</tr>
<tr>
<td>Temporal (T)</td>
<td>53.7±7.2</td>
<td>99.6±3.5</td>
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<td>Centroparietal (CP)</td>
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<td>94.7±4.0</td>
</tr>
<tr>
<td>Hemispheric mean</td>
<td>53.9±7.1</td>
<td>—</td>
</tr>
</tbody>
</table>

The results are presented as means ±SD; *p<0.05, **p<0.01, ***p<0.001, compared to controls (Student's t-test).

compared to the controls.

The correlation analysis between rCBF and the clinical symptoms in schizophrenic patients was performed. An inverse correlation between the frontal blood flow and negative symptoms was demonstrated. The lower the regional distribution value in the left frontal region, the more pronounced was the blunted affect on BPRS (p<0.01; Fig. 2). Scores of avolition-apathy and inattention on SANS tended to correlate inversely with the regional distribution value in the left frontal region (p<0.05). The lower left frontal flow distribution also tended to be associated with a poor performance on the Benton Visual Retention Test and the digit span on the Wechsler Memory Scale (p<0.05). Performance on the Wisconsin Card Sorting Test was significantly poorer in the schizophrenics than in the controls, but did not correlate with the frontal blood flow.

rCBF in schizophrenics was not correlated with age, educational level, duration of illness or antipsychotic medication level which was converted to chlorpromazine hydrochloride equivalents. Fig. 3 shows the relationship between the left frontal distribution value and the duration of illness.

In variables of CT measurements, the area of the anterior cerebral fissure tended to show
a loose negative correlation with the left hemispheric mean flow value and the regional distribution value in the left frontal region without statistical significance (p < 0.1).

DISCUSSION

In the present study, 39 schizophrenic patients showed decreased absolute values for rCBF in each brain region and reduced regional distribution values only in the left frontal region compared with the controls. The absolute values of rCBF vary widely among individuals and are influenced significantly by the arterial carbon dioxide levels. Therefore, it is advantageous to study the relative flow distribution such as the regional distribution value in order to evaluate rCBF.

In 1974, Ingvar and Franzén reported a decrease in the frontal blood flow in schizophrenic patients and an association between the reduced frontal blood flow and symptoms of indifference and inactivity. Thereafter, attention has been focused on reduced frontal activity, referred to as "hypofrontality" in schizophrenia. Using the $^{133}$Xenon inhalation technique or three-dimensional techniques such as positron emission tomography, several investigators have replicated the hypofrontality, although this has not been confirmed by others. Recently, more specific abnormalities to the prefrontal cortex in schizophrenia have been demonstrated by activation studies in which the regional brain activities are measured during performance of a task that activates the frontal lobes. The results of our present study performed under resting conditions suggest that schizophrenic patients have a basal defect in the frontal lobe function.

As symptoms resembling the negative symptoms characteristic of schizophrenia are frequently observed as a consequence of frontal lobe injury, it has been hypothesized that a decrease in the activity of the frontal lobes might account for the negative symptoms in schizophrenia. After Ingvar and Franzén, however, the correlations between the hypofrontality and clinical symptoms in schizophrenia have not been examined in detail. The present study indicates that the negative symptoms may be related to the left frontal lobe dysfunction.

The underlying neural mechanisms of the hypofrontality remain unknown. The tendency for a negative correlation observed between the left frontal blood flow and the area of the anterior cerebral fissure in some of our patients suggests the possibility that the hypofrontality may reflect structural abnormalities in the frontal lobe. Further investigations using techniques such as the single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) which have a higher degree of resolution may provide more precise information concerning the relationship between abnormal brain function and structure in schizophrenia.

ACKNOWLEDGMENT

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