Cerebral Blood Flow Velocity in Acute Schizophrenic Patients
A Transcranial Doppler Ultrasonography Study

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Background and Purpose—The aim of this study was to determine whether acutely psychotic first-episode schizophrenics show an increased cerebral blood flow velocity and whether this condition is reversible on psychopathological improvement.

Methods—In the first of two examinations, transcranial Doppler ultrasonography and assessment with the Positive and Negative Syndrome Scale (PANSS) were performed on 28 acutely psychotic, neuroleptically naive, first-episode schizophrenics. In the second examination, the same patients were assessed psychometrically (PANSS) as well as with Doppler ultrasonography after psychopathological improvement.

Results—Acutely psychotic first-episode schizophrenics showed a significant increase of the mean velocity on both sides in the middle and anterior cerebral arteries and in the right posterior cerebral artery. Blood flow showed significant correlations with productive psychotic symptoms. After psychopathological improvement there was a bilateral normalization of the mean velocity in the middle, anterior, and posterior cerebral arteries.

Conclusions—Acutely psychotic first-episode schizophrenics show a significantly increased bilateral cerebral blood flow velocity, which normalizes on psychopathological improvement. There were significant correlations of cerebral blood flow velocity with psychopathology. (Stroke. 1998;29:1149-1154.)

Key Words: blood flow velocity ■ cerebral blood flow ■ schizophrenia ■ ultrasonography, Doppler

Blood flow changes in schizophrenia have been demonstrated with SPECT and PET but with inconsistent findings. Most studies deal mainly with chronic schizophrenia, and the essential finding is hypoperfusion. Using 133Xe inhalation, Ingvar and Franzén were the first to report hypofrontality in schizophrenics. Some recent imaging studies on acute schizophrenia describe hyperperfusion in the supply areas of the MCA and the ACA, occasionally with a left-side predominance. An investigation of brain activity in schizophrenics depends on the profile of the particular target symptom and on how strongly it is pronounced in the patient group. Hoyer and Österreich found that acutely psychotic schizophrenics show an increase in global cerebral perfusion of about twice the normal value, whereas in chronic schizophrenics this parameter is significantly lower than in acute schizophrenics or healthy control subjects, without a significant difference between control patients and patients with paranoia or schizophrenia simplex. It should thus be possible to demonstrate a correlation between psychotic state and CBFV.

TCD is a standard method in neurology and neurosurgery but is not yet widely used in psychiatry, and no systematic neuropsychiatric studies have used this method. CBFV measurements by TCD show a high reliability and correlation with rCBF. TCD can locate vessels and quantify blood flow velocity with precision, thus allowing an accurate identification of the vessel irrigating the brain area in question. CBFV is the decisive Doppler parameter since flow velocity varies directly with the diameter of the small resistance vessels, whereas the diameter of the basal cerebral arteries remains essentially constant. Given that CBF equals CBFV times vessel diameter, where vessel diameter equals πr², then CBFV is a direct indicator of CBF. There are no known changes in vessel diameter in schizophrenia, since this condition in and of itself does not affect the blood vessels, and first-episode acute schizophrenic patients not suffering from other diseases will not, as a rule, show pathomorphological vessel changes.

It was the aim of this study to determine by means of TCD whether there is a difference in the CBFV of the basal cerebral arteries under resting conditions in acute schizophrenic patients and normal control subjects; whether this difference is reversible after psychopathological improve-
Subjects and Methods

Subjects
Subjects were 28 acutely psychotic, neuroleptically naive, first-episode schizophrenic patients, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and the International Classification of Diseases, Ninth Revision, and screened according to the usual exclusion criteria, ie, schizo-affective, bipolar mood, organic brain, or any general neurological or medical disorder; mental retardation; a history of severe head trauma, vascular-associated headache, substance abuse, or neuroleptic treatment; age <18 or >65 years; and pregnancy. Controls were 20 age-matched normal subjects. The mean age of patients was 33±12 years (15 male, 13 female), and that of control subjects (10 male, 10 female) was 32±10 years. Each patient gave informed consent and had extracranial and transcranial Doppler ultrasonography and a cranial CT scan done before inclusion into the study to screen out individuals with pathological findings. All patients and control subjects had normal blood pressure (systolic <140 mm Hg, diastolic <90 mm Hg). The first examination was done in the acute psychotic state and the second after neuroleptic treatment and psychopathological improvement, defined as a decrease of ≥50% of positive sum scores on PANSS. Choice of neuroleptic drugs and dosage depended exclusively on the individual target symptoms, which aimed at psychopathological remission. Patients were assessed psychometrically both times with PANSS,20 a 33-item scale with 1 to 7 points (normal to extremely abnormal) for each item and subscores for 7 positive, 7 negative, and 16 global psychopathological symptoms: delusions, formal thought disorders, hallucinations, agitation, grandiosity, suspiciousness/persecution, and hostility (P1 to P7); blunted affect, emotional withdrawal, poor rapport, social passivity and apathy, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking (N1 to N7); and health concerns, anxiety, guilt, tension, mannerisms and posturing, depression, motor retardation, uncooperative behavior, unusual thought contents, disorientation, poor attention, lack of judgment and insight, avolition, poor impulse control, self-centeredness, and active social avoidance (G1 to G16).

Transcranial Doppler Ultrasonography
For each examination, simultaneous bilateral isonation was done sequentially on the basal MCA, ACA, and PCA with a 2-MHz pulsed-wave transducer probe (Neurogad, Medasonics). The test-retest reliability found for the ACA, MCA, and PCA in the 20 healthy control subjects was 0.90<r<0.95. After resting for 5 minutes, patients and control subjects were isonated under standard resting conditions (supine position, eyes closed, darkened room).
significant increase in the left MCA (r = −0.58, P = 0.001) and with the ACAs (r = −0.51, P = 0.005), and a negative correlation with the left MCA (r = −0.52, P = 0.005). All other PANSS symptoms showed no significant correlation with the ACA, the MCA, or the PCA on either side.

After psychopathological improvement there was a significant (0.001 < P < 0.05) bilateral reduction in the Vmean (Figure), with decreases bilaterally in the MCA and the ACA. The PCA showed slightly significant changes on the right side. Flow velocities in all vessels examined (ACA, MCA, PCA) returned to normal levels and no longer differed significantly from those of normal subjects (Table 3). The PI showed a significant increase in the left MCA (+0.078); the other vessels showed a slight increase just below the level of significance.

**Discussion**

It is hypothesized that acute schizophrenics show a state of increased brain activity and therefore an increased metabolic rate. An increased metabolic rate requires an increased blood supply and therefore a greater flow volume. Blood flow velocity is directly related to flow volume.15 An increased velocity therefore implies a correspondingly greater blood volume, which in turn indicates increased brain activity.15 It may be argued that the increased CBFV seen in acute schizophrenics is due to vasoconstriction. However, vasoconstriction would considerably decrease brain perfusion, which in turn would result in lowered oxygenation and glucose supply; under such conditions, however, sustained activity is hardly possible. Furthermore, there is no pathomorphological evidence for vasoconstriction in schizophrenia. Studies on first-episode and unmedicated schizophrenics are few,26 and unlike studies with chronic schizophrenics, which exhibit hypoperfusion,26 most studies on acute schizophrenics have found a hyperperfusion in the frontotemporal region.5 This hyperperfusion correlates positively with at least some acute schizophrenic symptoms and their severity,30 as imaging studies have shown.3,5,28,31

This study is the first to demonstrate locally increased CBFV in first-episode acute schizophrenics against age-matched normal control subjects with the use of TCD. Increases were most pronounced in the MCA and the ACA on both sides. These vessels supply the frontal and the temporal lobes, which are actively involved in schizophrenia, where Catafau et al32 found a slightly higher flow on the left side. However, when we compared absolute values, our results show the same left-side tendency. The increased flow velocities correlated positively with acute psychotic symptoms as measured by PANSS. Positive correlations of acute psychotic symptoms and rCBF measured with 99mTc-HMPAO SPECT were also reported by Sabri et al28 and Silbersweig et al.30 After neuroleptic therapy and psychopathological improvement, brain activity returned to near-normal levels. The CBFV, although it remained marginally higher, also returned to within normal values. It would therefore seem that cerebral blood flow is a state (rather than a trait) marker.

In addition to the frontotemporal region, acutely psychotic schizophrenic patients show an increased blood flow in the posterior region.32 In the schizophrenic patients examined in this study, we also found marginally increased velocities in the PCA, which even showed a positive correlation with delusions. This would indicate that the occipital region is also actively involved in acute schizophrenia,33,34 and in our study we found that velocities in the PCA (which also irrigates the occipital region) show a marginal to significant increase relative to normal control subjects and a weakly significant decrease after psychopathological improvement.

Furthermore, associations between local blood flow changes and specific psychopathological syndromes indicate the areas of irritation affected. The negative correla-

| TABLE 2. PANSS-Doppler (Vmean) Correlations of Psychopathological Symptoms at First Examination (n=28) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Positive Sum Score | P1 | P5 | N6 | G7 |
| MCA (right) | r = 0.59 | r = 0.58 | r = 0.54 | … | … |
| P = 0.0009 | P = 0.001 | P = 0.003 | … | … |
| MCA (left) | … | … | … | r = −0.51 | r = −0.52 |
| … | … | … | P = 0.006 | P = 0.005 |
| MCA (both) | … | r = 0.52 | r = 0.54 | … | r = −0.58 |
| … | P = 0.005 | P = 0.003 | … | P = 0.001 |
| ACA (right) | r = 0.55 | r = 0.58 | … | … | … |
| P = 0.003 | P = 0.001 | … | … | … |
| ACA (both) | … | … | … | … | r = −0.51 |
| … | … | … | … | P = 0.005 |
| PCA (left) | … | r = 0.58 | … | … | … |
| … | P = 0.001 | … | … | … |

Positive sum score indicates sum score of all positive PANSS symptoms in percentages of maximum possible points. Positive symptoms include delusions (P1) and grandiosity (P5); negative symptoms; lack of spontaneity and flow of conversation (N6); global psychopathology, motor retardation (G7). Only significant values are shown (α = 0.05, β = 0.90).
tions for lack of spontaneity and flow of conversation to blood flow velocity in the left MCA could indicate an effect of decreased perfusion in the speech center. Vessels that do not supply this area showed no significant correlation. Motor retardation showed negative correlations bilaterally with both MCAs and ACAs, which supply the motor centers. Since the PCA does not irrigate this area, no correlations were found. These two findings show a direct correlation of changes in the activity of functions that have been mapped neuroanatomically, such as the speech or motor functions, with changes in the blood flow velocity of the artery supplying their brain areas.

Mapping specific psychopathological symptoms to a particular brain region has been difficult and not entirely free of controversy. However, we think that the findings in this study may contribute toward a clearer understanding of this approach. Delusions showed highly significant positive correlations with blood flow changes in the right MCA and ACA, and grandiosity showed highly significant positive correlations with blood flow changes in the MCA. Using 99mTc-HMPAO SPECT, Catafau et al described an increased rCBF in acutely psychotic schizophrenics bilaterally in the frontotemporal region. Sabri et al also found a bilateral rCBF increase in the frontotemporal region in acutely psychotic patients. A similar increase could be shown in ketamine- and psilocybin-induced experimental psychoses.35

There was a weak negative correlation of negative symptoms (assessed by PANSS) with the MCA. Thus, the more pronounced the negative symptoms, the lower are the CBFV values in the corresponding areas. Since negative symptoms in chronic schizophrenics correlate with hypoperfusion, it is interesting that we have found negative symptoms in acute schizophrenics to correlate with a lowered CBFV. It would be interesting to reexamine acute schizophrenic patients after a few years and then in the chronic stage of their illness to verify whether hyperperfusion first normalizes and then progresses to hypoperfusion.

Further studies are needed to clarify how TCD can be used in follow-up monitoring to identify and distinguish therapy responders from nonresponders and whether it can yield additional information on the course of therapy and possibly even be used as a predictor variable (warning signs). Since it relies only on physically measurable physiological parameters (unlike psychometric evaluation methods), TCD can contribute toward a more objective diagnosis of schizophrenia. An increase in the V\text{mean} could thus indicate a first or renewed exacerbation of illness. In high-risk individuals (first-degree relatives), onset of illness could be detected early by means of such an increase and so be treated while still in the early stages, thereby improving prognosis and shortening the hospital stay.
TABLE 3. \(V_{\text{mean}}\) and PI in the MCA, ACA, and PCA in 25 Schizophrenic Patients After Psychopathological Improvement

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
<th>Bilateral</th>
</tr>
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<tbody>
<tr>
<td>MCA</td>
<td>65 ± 11</td>
<td>64 ± 11</td>
<td>64 ± 10</td>
</tr>
<tr>
<td></td>
<td>(59 ± 13)</td>
<td>(59 ± 13)</td>
<td>(59 ± 13)</td>
</tr>
<tr>
<td>ACA</td>
<td>54 ± 11</td>
<td>52 ± 12</td>
<td>53 ± 10</td>
</tr>
<tr>
<td></td>
<td>(49 ± 12)</td>
<td>(49 ± 12)</td>
<td>(49 ± 12)</td>
</tr>
<tr>
<td>PCA</td>
<td>37 ± 6</td>
<td>37 ± 7</td>
<td>37 ± 5</td>
</tr>
<tr>
<td></td>
<td>(36 ± 8)</td>
<td>(37 ± 8)</td>
<td>(36 ± 8)</td>
</tr>
</tbody>
</table>

Values are mean ± SD, with normal values in parentheses, expressed in centimeters per second.

Further empirical studies are needed, particularly to evaluate the critical cutoff points (areas) to distinguish the various subgroups of schizophrenic patients regarding responders versus nonresponders.

This study suggests that, in addition to purely clinical fields such as neurosurgery and neurology, in which it has long been used, TCD also holds great potential for psychiatry. Thus, a new range of applications could open up for TCD, particularly in view of its high temporal resolution, which could be essential for examinations requiring real-time monitoring.

Conclusions

CBFV was shown to be a possible indicator of acute schizophrenia when acutely psychotic schizophrenic patients were compared with age-matched control subjects and schizophrenic patients after psychopathological improvement. Since it is noninvasive, TCD also allows practically unlimited repeated measurements for blood flow velocity status reports and follow-up; it is also readily available and requires little preparation. Furthermore, a combination of the high temporal resolution of TCD and the high spatial resolution of imaging procedures such as PET and SPECT may result in further understanding of the pathophysiological processes of mental illness and thus may contribute toward more effective therapy.

Acknowledgments

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