Middle Cerebral Artery Blood Velocity and Cerebral Blood Flow in Sickle Cell Disease

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To understand better the relationship between blood velocity measured by transcranial Doppler and cerebral blood flow measured by the $^{133}$Xe inhalation method, we examined 23 patients undergoing evaluation in the Comprehensive Sickle Cell Center at Columbia University. Blood velocity in the middle cerebral artery was directly related to cerebral flow ($r=0.77; p<0.05$). A multivariate analysis in this sample made it possible to improve this correlation to account for more than 90% of the variability in cerebral blood flow by the use of transcranial Doppler measures of velocity and pulsatility along with the patient's age and hematocrit ($r=0.95; p<0.001$). It is likely that the combination of Doppler and clinical or demographic variables in other diseases will similarly improve the quantitative estimation of cerebral blood flow. (Stroke 1991;22:27-30)

In 1982, the transcranial Doppler (TCD) ultrasound device was introduced which, by using a lower frequency probe, was able to record blood velocity from the basal cerebral arteries through an intact cranium.1 The TCD device is becoming accepted as a useful tool for the evaluation of intracranial stenosis, vasospasm, and the intracranial hemodynamics associated with occlusive carotid disease.2

Transcranial Doppler measures blood velocity, but it is not yet possible to measure intracranial vessel diameters reliably using ultrasound techniques, so direct calculations of cerebral blood flow (CBF) (mean arterial blood velocity x cross-sectional area) cannot be made. Few studies have explored the relationship between blood velocity, as measured by TCD, and CBF, and the correlations have been poor. We report our experience with the relationship between CBF, blood velocity, and related clinical indexes in patients with sickle cell disease.

Materials and Methods

We studied our patients as part of an ongoing prospective investigation of sickle cell anemia.3-4 Of the 100 patients entered into this registry at the time of this study, 25 patients were studied by TCD, 58 had regional CBF determination by the $^{133}$Xe inhalation technique, and 23 had both CBF and TCD studies. Nine of these 23 patients were men or boys; two had hemoglobin SC disease, one had hemoglobin S thalassemia disease, and the remainder had hemoglobin SS disease. The mean age was 23 years (range, 6-51).

Of the 23 patients included in this analysis, 20 had both the TCD and CBF determination performed on the same day, usually within 1 hour of each other. Blood pressure, hematocrit, and $P_{CO_2}$ were routinely measured at the time of the CBF study.

The Doppler device used (model TC2-64, EME, Ueberlingen, FRG) is a microcomputer-controlled directional Doppler operating at 2 MHz pulsed ultrasound, with a 64-point fast Fourier transform spectrum analyzer. The transcranial probe uses a focused beam operating at depths of 25-155 mm, electronically adjustable in steps of 5 mm; pulse repetition frequency is 5-10 kHz with a sound intensity range of 10-100 mW/cm², pulse length 13 μsec, gate width 13 μsec, vessel wall filter 150 Hz, and low pass filter 10 kHz. The output is displayed on a CRT screen as a plot of time versus Doppler shift. Results were stored

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Presented as part of the William McKinney Award presentation at the 11th Annual Meeting of the American Society of Neuroimaging, Tampa, Fla.

Supported in part by a gift from the Horace W. Goldsmith Foundation, Clinical Neuroscience Training Program contract NS-07155, contract NHLBI 1 N01 HB 7010, the Sickle Cell Center grant NHLBI HL-28381-01, and contract NS-2-2079 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, and gifts to the Yale Stroke Program.

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Received May 14, 1990; accepted September 5, 1990.
on a Tandy Model 100 computer (Tandy Corp., Ft. Worth, Tex.) using customized software from CUZN Consulting, New York.

Transcranial Doppler recordings were made of both middle cerebral arteries (MCAs). All studies were performed with the patient in bed and with the head elevated no more than 30°. Readings at depths of 45, 50, and 55 mm were used as the proximal MCA. The arithmetic mean of these six readings (three from each side) was used in all calculations. At each depth, the systolic velocity ($V_{systolic}$), mean velocity ($V_{mean}$), and systolic velocity-to-diastolic velocity ratio were recorded. From these data, the diastolic velocity ($V_{diastolic}$), pulsatility index (PI) ($[V_{systolic} - V_{diastolic}] / V_{mean}$), and pulsatility transmission index ($PI / P_{reference}$) were calculated.

Cerebral blood flow analysis was performed using the $^{133}$Xe inhalation method for determining flow on a Novo Cerebrograph 32c (Novo Diagnostic Systems, Copenhagen, Denmark) with 32 detectors. Compart-mental size variables were also calculated: $f_1$, fast-compartment (gray matter) flow, in milliliters per 100 grams per minute; $p_1$, fast-compartment (gray matter) weighting coefficient; $p_v$, vascular compartment size; and $pr_r$, ratio of vascular to fast-compartment size.

The rationale and our experience with these measurements in patients with sickle cell disease have been reported previously, as have the details of the technique and quality control procedures. The arithmetic mean of both hemispheres was used in the calculations; $f_1$ was used as the measure of CBF, derived with the six-unknown model.

Analysis included "best" model by forward, stepwise, and backward procedures using $F$ tests. Statistical analysis was performed on an Apple Maccintosh II using DATADESK PROFESSIONAL (Odesta Software, Northbrook, Ill.) and on an IBM System 2 PC using SAS Version 6 (Statistical Analysis System, Cary, N.C.).

Results

For the 23 patients studied, mean hematocrit was 25 (range, 10–38), mean systolic velocity in the MCA was 153 cm/sec (range, 68–289), and mean CBF was 124 ml/100 g/min (range, 64.9–193).

Ten of the 23 patients had abnormal magnetic resonance imaging (MRI) (usually suggesting distal field infarction), seven had a clinical history of stroke (all of these had abnormal MRI), and only four had clinical deficits (mild weakness) at the time of this study. One patient had clinical evidence for a new stroke within the month before her studies in this protocol. Three had received transfusion therapy, only one within a week of TCD and CBF examinations. Blood pressure readings were available for only 19 of the patients; mean systolic blood pressure was 121 mm Hg (range, 90–182), and mean diastolic blood pressure was 69 mm Hg (range, 48–112).

Angiographic information about the large vessels was not obtained as part of this protocol, and the number of patients with carotid disease or MCA stem disease is unknown. None of our patients had a focal increase in blood velocity in the MCA stem, suggestive of intracranial stenosis.

There was a correlation between hematocrit and blood velocity ($r = -0.638; p = 0.005$). A similar correlation was demonstrated for hematocrit and CBF ($r = -0.778; p = 0.001$). There were also fair correlations for the vascular compartment variables ($r = -0.632$ for $p_1$ [$p = 0.001$], $r = -0.773$ for $p_v$ [$p = 0.001$], and $r = -0.629$ for $pr_r$ [$p = 0.001$]). The hematocrit was weakly correlated with the pulsatility index ($r = 0.591; p = 0.05$).

We found a fair correlation between MCA velocity and CBF (Figure 1). There was little difference in the correlations between the systolic ($r = 0.774; p = 0.001$), mean ($r = 0.782; p = 0.001$), and diastolic velocities ($r = 0.713; p = 0.001$) with the CBF. The correlation coefficients for the TCD recordings, measures of CBF, and clinical information are summarized in Table 1.

The pulsatility index was weakly correlated with CBF ($r = -0.448; p = 0.05$). There was a tendency for lower pulsatilities in patients with an abnormal MRI, but this association did not reach statistical significance.

We used a "best" model by forward, stepwise, and backward procedures to predict CBF. Initially, all variables except for systolic and diastolic blood pressure (23 patients) were used, then a second analysis was performed with all variables (19 cases). With this analysis, only the systolic and diastolic velocities, hematocrit, age, and pulsatility index entered the model. The equation for CBF = 1.36$V_{systolic}$ − 2.04$V_{diastolic}$ − 2.99hematocrit − 0.828age − 151PI +282 was able to predict more than 90% of the variability in CBF. This model was highly significant ($r = 0.947; p = 0.001$). Table 2 summarizes the results of this regression.

Discussion

This study confirms the increased CBF reported in sickle cell disease and demonstrates a similar effect...
TABLE 1. Pearson Correlation Coefficients for Clinical, Transcranial Doppler, and Cerebral Blood Flow Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>( f, )</th>
<th>( V_s )</th>
<th>( V_m )</th>
<th>( V_d )</th>
<th>( P_l )</th>
<th>Age</th>
<th>Hct</th>
<th>SyBP</th>
<th>DiBP</th>
<th>ISI</th>
<th>( p_1 )</th>
<th>( p_4 )</th>
<th>( p_{4s} )</th>
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<tbody>
<tr>
<td>( f, )</td>
<td>1.000</td>
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<td></td>
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<tr>
<td>( V_s )</td>
<td>0.774*</td>
<td>1.000</td>
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<tr>
<td>( V_m )</td>
<td>0.782*</td>
<td>0.983*</td>
<td>1.000</td>
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<tr>
<td>( V_d )</td>
<td>0.713*</td>
<td>0.947*</td>
<td>0.982*</td>
<td>1.000</td>
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<tr>
<td>( P_l )</td>
<td>-0.448‡</td>
<td>-0.420‡</td>
<td>-0.563‡</td>
<td>-0.648‡</td>
<td>1.000</td>
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<td></td>
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<tr>
<td>Age</td>
<td>-0.320</td>
<td>-0.257</td>
<td>-0.263</td>
<td>-0.247</td>
<td>0.106</td>
<td>1.000</td>
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<tr>
<td>Hct</td>
<td>-0.788*</td>
<td>-0.638‡</td>
<td>-0.694*</td>
<td>-0.683*</td>
<td>0.591†</td>
<td>-0.037</td>
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<td>SyBP</td>
<td>-0.288</td>
<td>-0.022</td>
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<td>DiBP</td>
<td>-0.437‡</td>
<td>-0.243</td>
<td>-0.237</td>
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<td>0.007</td>
<td>0.493‡</td>
<td>0.366</td>
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<td>ISI</td>
<td>0.943*</td>
<td>0.703*</td>
<td>0.708*</td>
<td>0.629*</td>
<td>-0.383‡</td>
<td>-0.511‡</td>
<td>-0.638‡</td>
<td>-0.397‡</td>
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<td>( p_1 )</td>
<td>0.938*</td>
<td>0.726*</td>
<td>0.717*</td>
<td>0.631*</td>
<td>-0.292</td>
<td>-0.498‡</td>
<td>-0.632*</td>
<td>-0.336</td>
<td>-0.505‡</td>
<td>0.967*</td>
<td>1.000</td>
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<tr>
<td>( p_4 )</td>
<td>0.909*</td>
<td>0.762*</td>
<td>0.794*</td>
<td>0.768*</td>
<td>-0.572‡</td>
<td>-0.303</td>
<td>-0.773*</td>
<td>-0.136</td>
<td>-0.319</td>
<td>0.817*</td>
<td>0.814*</td>
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<td></td>
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<tr>
<td>( p_{4s} )</td>
<td>0.661‡</td>
<td>0.536‡</td>
<td>0.582‡</td>
<td>0.593‡</td>
<td>-0.572‡</td>
<td>-0.074</td>
<td>-0.629*</td>
<td>0.079</td>
<td>-0.072</td>
<td>0.483‡</td>
<td>0.429‡</td>
<td>0.846*</td>
<td>1.000</td>
</tr>
</tbody>
</table>

\( f, \) cerebral blood flow; \( V_s, \) systolic velocity; \( V_m, \) mean velocity; \( V_d, \) diastolic velocity; \( P_l, \) pulsatility index; Hct, hematocrit; SyBP, systolic blood pressure; DiBP, diastolic blood pressure; ISI, initial slope index; \( p_1, \) fast-compartment weighting coefficient; \( p_4, \) vascular compartment size; \( p_{4s}, \) ratio of vascular to fast-compartment size.

*†‡\( p<0.001, 0.05, 0.10, \) respectively.

TABLE 2. Results of Regression Model for Cerebral Blood Flow

| Variable | Coefficient | Standard error | \( F \) | Probability=\( F \) \( p \) value |
|----------|-------------|----------------|------|------------------|-----|
| Constant | 282         | 42.7           | 43.71| 0.0001           | 0.0001|
| \( V_m \) | 1.36        | 0.308          | 9.27 | 0.0073           | 0.0001|
| \( V_d \) | -2.04       | 0.543          | 21.37| 0.0002           | 0.0112|
| Hct      | -2.99       | 0.646          | 19.60| 0.0004           | 0.0485|
| Age      | -0.828      | 0.272          | 14.14| 0.0016           | 0.0496|
| \( P_l \) | -151        | 57.3           | 6.92 | 0.0176           | 0.0663|

\( R^2=89.6\%; \) \( r=0.947, \) \( s=13.91 \) with 17 degrees of freedom (df) (23 observations). For regression, df=5 and \( F \) ratio=29.2; for residual, \( F \) ratio=17.
Hematocrit explains approximately 62% of CBF variability. For coarse estimates, therefore, no other measurements are necessary in this circumstance. However, the addition of several TCD variables and age raises the proportion of explained variance to more than 90%. In this population, TCD thus can improve the prediction of CBF by this amount over the hematocrit alone and allows for finer distinction and more precise follow-up. It is likely that the introduction of TCD to other clinical or demographic variables in other diseases will contribute similarly.

References

KEY WORDS • blood flow velocity • anemia, sickle cell • cerebral blood flow • ultrasonics