Arterial Oxygen Content and Age Are Determinants of Middle Cerebral Artery Blood Flow Velocity

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**Background and Purpose:** Transcranial Doppler blood flow velocities are inversely related to age and hematocrit, but the relative importance of age, oxygenation, and hemorheological factors has not previously been examined. We evaluated the relative contributions of these factors to middle cerebral artery blood flow velocity in adults with chronic renal failure, a population subject to significant fluctuations in hematologic profile.

**Methods:** Twenty-six subjects were studied, with arterial shunt blood sampled at the time of transcranial Doppler before dialysis. Twenty subjects from the original cohort were studied twice to examine the effects of intraindividual changes in blood oxygenation and rheology on Doppler velocities.

**Results:** Age \((r=-.61, P<.001)\), high-shear viscosity \((r=-.46, P<.82)\), and arterial oxygen content \((r=-.44, P<.05)\) were all inversely related to middle cerebral artery blood flow velocity. Age was the strongest velocity predictor, accounting for 37% of variance by simple regression analysis. Intraindividual change in arterial oxygen content explained most (54%) of the middle cerebral artery blood flow velocity variation between studies \((r=-.74, P<.001)\). Multiple regression analysis showed that inclusion of additional variables could not account for more velocity variation than change in arterial oxygen content alone.

**Conclusions:** In this population, age and arterial oxygen content were the most important determinants of interindividual middle cerebral artery blood flow velocity variance and intraindividual middle cerebral artery blood flow velocity variation, respectively. (*Stroke* 1993;24:1025-1028)

**KEY WORDS** • aging • cerebral circulation • Doppler

Transcranial Doppler is an ultrasound technique allowing noninvasive measurement of basal cerebral artery blood flow velocities.\(^1\) Hemodynamic factors including vessel lumen dimensions, compliance, and pressure gradients are major velocity determinants.\(^2\) Other factors related to blood flow velocity include age, arterial \(\text{PCO}_2\),\(^3,5\) hematocrit, and fibrinogen level.\(^6\) Hematocrit and fibrinogen level may influence transcranial Doppler blood flow velocities through their effects on whole blood and plasma viscosity, respectively.\(^7,6\) Some cerebral blood flow (CBF) studies suggest that arterial oxygen content is a fundamental CBF determinant, perhaps more important than blood viscosity.\(^7,8\) Ameriso et al\(^9\) found that whole blood viscosity only partly explained the inverse relation between hematocrit and middle cerebral artery (MCA) blood flow velocity in a young adult population and suggested that blood oxygenation may be contributory.

The present study examined the relative contributions of age, selected hemorheological factors, and blood oxygenation as determinants of MCA blood flow velocity in adults with chronic renal failure. This population was selected for ease of access to arterial shunt blood and because they are subject to significant changes in hematologic profile as a result of anemia of chronic renal failure and changes in fluid status. Hemodialysis-dependent renal failure subjects, when studied on two separate occasions before routine dialysis, thus served as a model to evaluate the effects of intraindividual fluctuations in blood gases and hemorheological factors on MCA blood flow velocity.

**Subjects and Methods**

Subjects consisted of ambulatory adult volunteers with chronic renal failure who attended the University of Southern California (USC) Dialysis Out-Patient Center. Participants were free of acute illness at the time of study and had no known cerebrovascular disease as determined by history, physical, and neurological examination. Stroke risk factors were defined by standard criteria.\(^10\) This study was performed in accordance with guidelines of the USC Investigational Review Board.
MCA blood flow velocities were measured with a 2-MHz pulsed-wave, range-gated Doppler system (Transpect TCD; Medasonics, Mountain View, Calif) through the temporal window using a 4-second sweep time as previously described. Averaged values for MCA peak velocity, mean velocity, diastolic velocity, and pulsatility index (peak velocity minus diastolic velocity divided by mean velocity) were calculated from six readings representing the three maximal reflected MCA signals from each side. Only subjects without transcranial Doppler evidence of stenosis and with bilaterally adequate MCA signals consisting of flow coming toward the probe at a depth of 35 to 55 mm were included. Doppler studies were performed before dialysis, thus avoiding the acute effects of hemodialysis on MCA blood flow velocity.11 During transcranial Doppler examinations, subjects were supine with head elevated 30 degrees, resting comfortably with eyes closed, and ventilating normally. All but one of the studies were performed by the same examiner (R.F.M.). In our laboratory, intraobserver and interobserver MCA blood flow velocity variabilities are 4% and 5%, respectively.

Carotid Doppler ultrasonography to screen for extracranial carotid artery stenosis was performed using a portable 5.4-MHz continuous-wave system (Transpect TCD; Medasonics). Subjects with blood flow velocities suggestive of carotid stenosis underwent duplex examination (model DRF 400, Diasonics, Milpitas, Calif) in the Los Angeles County–USC Noninvasive Vascular Laboratory.1,13

Arterial shunt blood was obtained within 20 minutes of Doppler examination by sterile puncture for complete blood count, hemorheological measurements, and blood gas determinations. Hemoglobin level, hematocrit, and white blood cell and platelet counts were determined from ethylenediaminetetraacetic acid (EDTA)-anticoagulated samples (1.5 mg/mL) using an automated hematology analyzer (Mimics STX, Roche Diagnostics, Inc, Belville, NJ). Plasma fibrinogen was determined from EDTA-anticoagulated samples based on the turbidimetric rate of fibrin polymer formation (Du Pont ACA, Wilmington, Del). Whole blood viscosity at high and low shear rates (94.5 and 1.3 seconds^-1) was measured at 25°C using a small-volume Couette viscometer (model LS-30, Contraves AG, Zurich, Switzerland) with appropriate corrections for torque decay at the low shear rate. Plasma viscosity was measured at 25°C using a plasma viscometer (Haake Mess Technik GmbH, Karlsruhe, Germany). Arterial shunt samples for blood gas analysis were collected directly into a heparinized syringe (40 U/mL, Quik AGB, Marquest Medical Products, Englewood, Colo) and placed in an ice bath. Direct measurements of arterial oxygen saturation, PCO₂, and pH at 37°C were made within 20 minutes of phlebotomy using an automated blood gas analyzer (ABL 30, Radiometer, Copenhagen, Denmark). Arterial oxygen content was calculated from the product of hemoglobin times fractional oxygen saturation.

Simple linear and stepwise multiple regressions were used to analyze associations between variables and MCA blood flow velocity and between variables themselves. Both the absolute values of change and percent change were calculated to examine intraIndividual changes in variables between examinations.

### Table 1. Baseline Study of 26 Subjects With Simple Regression Analysis of Mean Middle Cerebral Artery Blood Flow Velocity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
<th>Range</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>51±16</td>
<td>19-69</td>
<td>- .61*</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>27.8±3.7</td>
<td>22.1-38.3</td>
<td>- .49†</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.0±1.3</td>
<td>7.0-12.3</td>
<td>- .49†</td>
</tr>
<tr>
<td>Whole blood viscosity, high shear (cp)</td>
<td>4.5±1.2</td>
<td>2.6-10.0</td>
<td>- .46f</td>
</tr>
<tr>
<td>Arterial oxygen content (mL/100 mL)</td>
<td>12.2±1.6</td>
<td>9.5-16.4</td>
<td>- .44†</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>360±78</td>
<td>241-521</td>
<td>- .40†</td>
</tr>
<tr>
<td>Whole blood viscosity, low shear (cp)</td>
<td>12.1±7.0</td>
<td>6.4-33.9</td>
<td>- .35</td>
</tr>
<tr>
<td>Plasma viscosity (cp)</td>
<td>1.64±0.1</td>
<td>1.54-1.98</td>
<td>- .27</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>92±31</td>
<td>62-130</td>
<td>- .26</td>
</tr>
<tr>
<td>Arterial PCO₂ (mm Hg)</td>
<td>39.2±4.0</td>
<td>33-45</td>
<td>- .08</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.36±0.05</td>
<td>7.27-7.44</td>
<td>- .26</td>
</tr>
<tr>
<td>Arterial PO₂ (mm Hg)</td>
<td>97.6±16.0</td>
<td>54-132</td>
<td>.16</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>96.7±2.4</td>
<td>87-99</td>
<td>.05</td>
</tr>
</tbody>
</table>

*<P<.001, †P<.02, ‡P<.05 different from zero.

### Results

We studied 26 subjects with chronic renal failure (15 men and 11 women; mean±SD age, 51±16 [range, 19 to 69] years). Stroke risk factors present in this population included 8 subjects with diabetes mellitus, 4 smokers, 2 subjects with atherosclerotic heart disease, and 1 with systemic lupus erythematosus. Most (22/26) had a prior history of hypertension, but only 8 had current hypertension as defined by blood pressures greater than 140/90 mm Hg on two recent occasions. Twenty-five subjects were receiving erythropoietin treatment for anemia of chronic renal failure.14 Transcranial Doppler values for peak systolic (111±25 cm/s [mean±SD]; range, 68 to 168 cm/s) and mean MCA blood flow velocities (72±18 cm/s; range, 45 to 111 cm/s) were highly correlated (r= .89, P<.0001).

Baseline data and correlation coefficients between individual variables and mean MCA blood flow velocity for the initial study are shown in Table 1. Simple regression analysis revealed six variables with significant inverse relation to mean MCA blood flow velocity. Age was the strongest interindividual MCA blood flow velocity correlate and was unrelated (P>.05) to the other five significant parameters shown in Table 1; age was also unrelated to mean blood pressure. Pulsatility index demonstrated a strong positive correlation to age (r=.60, P<.002). High-shear whole blood viscosity was the strongest hemorheological correlate to MCA blood flow velocity, while arterial oxygen content was the only significantly related blood gas-derived parameter. Multiple regression analysis revealed that arterial oxygen content and age together explained 56% of the mean interindividual MCA blood flow velocity variance (r=- .75, P<.004).

Repeat examinations 79±58 days later included 20 of the original cohort, with dropout due to medical illness (n=2), renal transplant (n=1), and loss to follow-up (n=3). Mean age in the follow-up study was 53±15 years (range, 19-69 years). Extracranial carotid Doppler studies were performed on 15 of these subjects. Five subjects were unavailable for extracranial carotid study.
### Table 2. Intraindividual Mean Middle Cerebral Artery Blood Flow Velocity Variation: Simple Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔValues</th>
<th>PercentΔ</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial oxygen content (mL/100 mL)</td>
<td>1.2±0.9</td>
<td>9.6±7.2</td>
<td>-.74*</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>1.1±0.7</td>
<td>11.9±7.0</td>
<td>-.62†</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>3.7±2.7</td>
<td>12.9±9.4</td>
<td>-.59‡</td>
</tr>
<tr>
<td>Whole blood viscosity, high shear (cp)</td>
<td>0.84±0.59</td>
<td>19.2±13.5</td>
<td>-.49‡</td>
</tr>
<tr>
<td>Whole blood viscosity, low shear (cp)</td>
<td>5.0±3.7</td>
<td>46.3±34</td>
<td>-.39</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>1.3±1.2</td>
<td>1.2±1.1</td>
<td>-.25</td>
</tr>
<tr>
<td>Plasma viscosity (cp)</td>
<td>0.085±0.081</td>
<td>5.2±5.0</td>
<td>.22</td>
</tr>
<tr>
<td>Arterial P0₂ (mm Hg)</td>
<td>12±10</td>
<td>12±10</td>
<td>-.16</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>0.04±0.03</td>
<td>0.4±0.33</td>
<td>-.09</td>
</tr>
<tr>
<td>Arterial PCo₂ (mm Hg)</td>
<td>3.3±2.2</td>
<td>8.3±5.7</td>
<td>.08</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>63.9±54.6</td>
<td>19.2±16.4</td>
<td>-.006</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>9.4±6.9</td>
<td>9.9±7.3</td>
<td>-.33</td>
</tr>
</tbody>
</table>

Values are mean±SD (n=20). Δ. Change in variable between examinations. r represents association between intraindividual percent Δ in middle cerebral artery velocity and percent Δ in variable.

*P<.001, †P<.01, ‡P<.03 different from zero.

Two subjects had mild unilaterally increased Doppler velocities; both had normal duplex examinations and were thus considered free of hemodynamically significant extracranial carotid disease.

Intraindividual changes in peak systolic (10.9±9.9% [mean±SD]) and mean MCA blood flow velocities (9.2±7.5%) between examinations were strongly related (r=.92, P<.0001). Absolute values of intraindividual change in mean middle cerebral artery blood flow velocity are presented in Table 2. Intraindividual change in arterial oxygen content explained 54% of mean MCA blood flow velocity variation (Figure), whereas high shear whole blood viscosity, the only significant hemorheological factor, accounted for only 24% as determined by simple regression analysis. Inverse relations of intraindividual changes in hemoglobin and hematocrit to mean MCA blood flow velocity variation were not as strong as that of arterial oxygen content, and no other variables were found to be significant. Multiple regression analyses showed no combination of variables could significantly account for more intraindividual MCA blood flow velocity variation than change in arterial oxygen content alone.

### Discussion

Arterial oxygenation and hemorheological factors have been postulated to explain the inverse relation between hematocrit and cerebral blood flow velocity. To the best of our knowledge, simultaneous direct measurement of these variables has not been performed in prior transcranial Doppler investigations. We directly measured critical hemorheological factors and blood gas variables sampled from arterial shunt blood in subjects with chronic renal failure at the time of Doppler examination before dialysis, and found that hematocrit, high-shear whole blood viscosity, and fibrinogen level all demonstrated significant inverse relations to MCA blood flow velocity. In addition, we report a significant inverse relation between arterial oxygen content and intraindividual MCA blood flow velocity. This study confirms the findings of Ameriso et al4 that high-shear whole blood viscosity in a young adult population accounted for only part of the hematocrit–MCA blood flow velocity inverse relation.

Age also inversely correlated to MCA blood flow velocity and was the strongest interindividual velocity predictor in this population. Further, our results indicate that the age–MCA velocity inverse relation was independent of systemic blood pressure, hematocrit, blood oxygenation, and hemorheological factors. Age was also the only variable that demonstrated a positive correlation to pulsatility index (r=.60, P<.001). Lower MCA blood flow velocity and higher pulsatility index are Doppler findings compatible with increased distal resistance15 and may indicate increasing cerebrovascular resistance with advancing age.16,17 The age–MCA velocity inverse relation is similar to Xenon inhalation studies showing CBF reduction with advancing age.18 The presence of stroke risk factors alone, as well as in an additive manner with normal aging, is also associated with reduced regional CBF; this is attributable in part to increased cerebrovascular resistance.18,19

Although volunteers in this study were without known cerebrovascular disease, patients with chronic renal failure do not represent a normal population, particularly with respect to presence of stroke risk factors. An important question is to what extent these findings in subjects with chronic renal failure may be generalized to the non–renal failure population. Inverse relations of MCA blood flow velocity with hematocrit, fibrinogen, and high-shear whole blood viscosity demonstrated in subjects with renal failure are in agreement with prior Doppler studies. The slope of the linear plot of hematocrit versus MCA blood flow velocity in our population was consistent with that found by Brass et al in the comparable hematocrit range. Fibrinogen level was independently inversely related to interindividual MCA blood flow velocity in subjects with renal failure, as previously described in an elderly population without known cerebrovascular disease. A strong age–MCA velocity inverse relation was also demonstrable in subjects with renal failure, as has been shown in non–renal failure populations. Therefore, our current findings likely indicate regulatory mechanisms for CBF velocity that are important in other populations.
We found that change in arterial oxygen content was the primary determinant of intraindividual MCA blood flow velocity variation. Brown et al.7,8 examined high-shear blood viscosity and arterial oxygen content in subjects with anemia, polycythemia, and paraproteinemia and found arterial oxygen content more important than viscosity as a determinant of CBF. Our results, in agreement with these prior investigations, demonstrated that changes in arterial oxygen content were stronger predictors of MCA blood flow velocity variation than hemorheological factors in nonischemic brain. In contrast, Korosue and Heros20 demonstrated that progressive hemodilution and hypoxic hypoxia had similar effects, augmenting CBF in normal rabbit brain; in ischemic brain, however, only hemodilution retained its effect of increasing CBF. Rheological factors may likewise be of greater importance than blood oxygenation as determinants of CBF velocity in ischemic brain, where vasodilatation is maximal and autoregulation impaired. Intact autoregulation dependent on a fundamental oxygen-sensitive mechanism has been hypothesized to explain the inverse association of CBF with arterial oxygen content.7,21,22 Cerebral oxygen delivery is the product of CBF and arterial oxygen content; thus, maintenance of oxygen delivery may account for the CBF–arterial oxygen content inverse relation and may also explain the inverse relation between transcranial Doppler cerebral blood flow velocities and blood oxygenation.

Acknowledgments
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