Sickle Cell Disease and Transcranial Doppler Imaging
Inter-Hemispheric Differences in Blood Flow Doppler Parameters

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Background and Purpose—To establish reference values of interhemispheric differences and ratios of blood flow Doppler parameters in the terminal internal carotid artery, middle cerebral artery, and anterior cerebral artery in children with sickle cell anemia.

Methods—Fifty-seven out of 74 recruited children (mean age, 7.8±3.4 years; range limits, 3–14 years), who were free of neurological deficits and intracranial narrowing detectable by MRA and had flow velocities <170 cm/s by conventional transcranial Doppler ultrasound, underwent transcranial color-coded duplex ultrasonography. Reference limits of flow parameters corrected and uncorrected for the angle of insonation were estimated using tolerance intervals, with P=0.90 for all possible data values from 95% of a population.

Results—Reference limits for left-to-right differences in cm/s in the mean angle-corrected and uncorrected flow velocities were −56 to 53 and −72 to 75 for middle cerebral artery, −49 to 57 and −81 to 91 for anterior cerebral artery, and −55 to 64 and −73 to 78 for terminal internal carotid artery, respectively. Respective reference limits for left-to-right velocity ratios were 0.31 to 1.84 and 0.38 to 1.75 for middle cerebral artery, 0.48 to 2.99 and 0.46 to 2.89 for anterior cerebral artery, and 0.61 to 2.56 and 0.56 to 2.23 for terminal internal carotid artery.

Conclusions—The study provides reference limits of interhemispheric differences and ratios of blood flow Doppler parameters that may be helpful in identification of intracranial arterial narrowing in children with sickle cell disease undergoing ultrasound screening for stroke prevention. (Stroke. 2011;42:81-86.)

Key Words: blood flow ▪ sickle cell disease ▪ sonography ▪ stroke ▪ transcranial Doppler

Children with sickle cell disease (SCD) are at high risk for stroke.1–3 The risk is highest in children with elevated blood flow velocity in the distal internal carotid (terminal internal carotid artery) or proximal middle cerebral artery (MCA), as measured with transcranial Doppler ultrasonography (TCD).4 Chronic blood transfusions, if implemented in a timely fashion in those with flow velocity >200 cm/s, can reduce the risk of stroke by as much as 92%.2 The use of a single TCD velocity alone to stratify future risk of stroke is limited, as shown by the fact that 60% of patients with velocities in the high-risk range who did not receive chronic transfusion therapy remained stroke-free over the subsequent 40 months.3,5 Also, single-flow velocity measurement from an artery cannot differentiate arterial stenosis from hyperemia.6–8 Children with hyperemia may not have the same risk-to-benefit ratio from indefinite transfusions as those with arterial stenosis.

The STOP investigators suggested that unilateral high-flow velocity indicates stenosis, whereas bilateral high-velocity represents bilateral stenosis, hyperemia, or both.2,9 Substantial side-to-side differences in flow velocities in individual children without any arterial narrowing,10 however, indicate that extrapolation of average group symmetry in flow velocities to individual children with SCD may not be correct.

There is potential to improve the ultrasound screening by using reference tolerance limits of interhemispheric differences in flow velocities in major brain arteries. These tolerance limits can inform an investigator what side-to-side differences in blood flow Doppler parameters can occur in children with SCD without hyperemia or evidence of arterial narrowing. Thus, the goal of our study was to establish such reference tolerance limits for transcranial color-coded duplex ultrasound parameters based on data from children with SCD who were not administered chronic transfusion therapy, who...
Materials and Methods

Study Group

Institutional Review Board of the Children’s Hospital of Philadelphia approved the protocol of this prospective cross-sectional study, which was also compliant with Health Insurance Portability and Accountability Act. Our cohort was recruited within the frame of the SCD Children Ongoing Radiological Evaluation Study sponsored by the National Institute of Health. Written informed consent was obtained from parents (with assent for children 7 years of age and older). The study group was drawn from the Comprehensive Sickle Cell Center at Children’s Hospital of Philadelphia using the following inclusion criteria: (1) homozygous for the sickle cell gene, confirmed by DNA-based mutational analysis; (2) age 2 to 14 years; (3) absence of localizing abnormalities on neurological examination indicating previous vascular territory ischemic injury; and (4) no history of stroke. Exclusion criteria were: (1) history of major head injury; (2) history of seizure disorder requiring anticonvulsant therapy; (3) active chronic transfusion or hydroxyurea therapy; (4) mean flow velocity >170 cm/s in any intracranial artery on a routine TCD screening examination at the time of study entry.

Study Procedures

A pediatric neurologist performed a baseline neurological examination on each child who fulfilled inclusion criteria. The examination included language, cranial nerves, sensorimotor ability and coordination, and the physical and neurological examination of soft signs. All children were subsequently scheduled for TCD and MRA examinations. Hemoglobin concentration and hematocrit level were obtained during well visits close in time to ultrasound studies.

MRA

To exclude children with intracranial arterial narrowing, we performed time-of-flight 3-dimensional gradient-echo sequence (repetition time/echo time = 28/3.28 ms; flip angle, 25°; matrix, 512x448) imaging on a 3-T scanner (Siemens Trio) covering the extracranial and intracranial arteries in the axial plane. Raw data from time-of-flight MRA were transferred to an online workstation for the generation of segmented 2-dimensional arterial reprojections using a commercially available maximum intensity projection ray trace and multiplanar reconstruction algorithms. The segmented 2-dimensional reprojections and raw data were displayed on a 1 024x1 024-pixel workstation and arteries were evaluated independently by 2 pediatric neuroradiologists (E.R.M. with 15 years and R.Z. with 25 years of experience in angiography) unaware of the ultrasound findings. Each evaluated all studies, and discrepancies were resolved by consensus. No extracranial arterial narrowing was identified in any of patients. The neuroradiologists excluded 7 children with intracranial arterial narrowing and 4 with degraded MRA attributable to motion artifacts. An additional 6 children did not complete MRA examinations.

Imaging Ultrasound Studies

Transcranial color-coded duplex sonography (sonographic scanner HDI 5000 with 1.8–3.6 MHz probe; Philips) studies were performed by 1 of 3 sonographers, each with >3 years of experience. Children were not permitted to sleep during examinations and were not sedated. The terminal internal carotid artery, M-1 MCA, and A1 segment of the anterior cerebral artery were identified via temporal acoustic windows using published standards. The mean time-averaged maximum (V_MN), hereafter referred to as mean flow velocity, peak systolic velocity (V_PS), and end diastolic velocity (V_ED) were calculated by automatic tracing of the Doppler waveform. Pulsatility index and resistivity index were calculated as follows: pulsatility index = (V_PS – V_ED)/V_MN and resistivity index = (V_PS – V_ED)/V_PS.

Statistical Analysis

We used statistical software SYSTAT 12 (SYSTAT Software Inc.), GraphPad free software (GraphPad software; http://www.graphpad.com), and R statistical computing software (http://www.r-project.org) to analyze data. Flow velocities were treated for outliers using Grubb T-statistics at α level <0.05. Outliers, if present, were not considered while checking for normality using Lilliefors test, provided by SYSTAT. Because data were normally distributed, the values from hemispheres were first compared using a paired 2-sided t test. We used Pearson correlation coefficient (r) to quantify bilateral relationships between Doppler parameters, and we used a nonpaired 2-sided t test to compare Doppler values between genders. To obtain transcranial color-coded duplex sonography velocities that are closer to velocities obtained with conventional TCD, we multiplied the angle-corrected velocities by the cosine of the angle of insonation. The resulted velocity values are hereafter referred to as “uncorrected” velocities.
We used estimates of tolerance interval, within which are included with probability of 0.90 all possible data values from 95% of a population to determine reference ranges of interhemispheric differences and ratios in Doppler parameters.\textsuperscript{13} Interhemispheric differences in Doppler parameters followed Gaussian distribution, and thus we calculated Gaussian tolerance interval. If L1 and L2 are the lower and upper limits of the interval, then $L_1 = \mu - k_s$ and $L_2 = \mu + k_s$, where values of $k$ were taken from article by Weissberg-Beatty\textsuperscript{14} ($\mu$=mean, $s$=standard deviation). For interhemispheric ratios in Doppler parameters, we calculated nonparametric tolerance intervals based on the Wilks method.\textsuperscript{15}

Multivariable linear regression analysis was used to determine associations, if any, of interhemispheric differences or ratios in blood flow Doppler parameters with age and gender after adjustment for hemoglobin or hematocrit. $P<0.05$ was considered significant.

### Results

There were 57 children (mean age, 7.7±3.4 years; range limits, 3–14 years; 32 females, 25 males) with complete evaluable data. Measurements of hematocrit level and hemoglobin concentrations were taken, on average, 21±6 days (range limits, 0–62 days) from the sonographic study. For 8 children without recent laboratory values, we used the average hemoglobin and hematocrit from the previous 3 visits (mean, 140±70 days; range limits, 73–386 days).

Values of angle-corrected blood flow Doppler parameters were, on average, 20% higher than uncorrected values, and differences were significant (Table 1). No outliers were found in values of blood flow velocities. Variability of angle-corrected velocity values was lower than variability of uncorrected velocities. The variability of impedance indexes was lower than variability of velocity values, and subsequently tolerance intervals were narrower, especially for the values calculated based on angle-corrected velocities (Table 1).

Correlation coefficients for Doppler parameters between sides were statistically significant for both angle-corrected and uncorrected values (Table 2). For uncorrected values, $r$ varied from 0.30 to 0.59, whereas for angle-corrected values $r$ ranged from 0.33 to 0.68 (Table 2).

No statistically significant side-to-side differences were found in any Doppler parameter in any artery. Average differences for the mean flow velocities were close to zero for both corrected and uncorrected values in all arteries; however, in general, left velocities were usually slightly higher than right ones (Table 3). Also the interhemispheric differences in impedance indexes were close to zero for the respective arteries (Table 3). Slightly lower impedance indexes were found in the left MCA and terminal internal carotid artery (Table 3). The tolerance interval for absolute differences between sides in the mean flow velocities in the MCA varied from 72 cm/s to 75 cm/s for uncorrected values and 53 cm/s to 56 cm/s for angle-corrected values, respectively (Table 3, also see the Figure). For other arteries, the width of the tolerance limits was greater for uncorrected values of the velocity differences, 81 cm/s to 91 cm/s for the anterior cerebral artery and 73 cm/s to 78 cm/s for the terminal internal carotid artery (Table 3). Tolerance limits tend to be asymmetrical; for instance, in the terminal internal carotid artery the limit of the mean velocity on the right side is 64 cm/s. The difference is still considered “normal” compared to respective velocity on the left side, whereas the velocity on the left side compared to the velocity on the right side is considered “normal” if the difference is not $>55$ cm/s (Table 3). Tolerance limits for impedance indexes showed the same asymmetrical pattern. Tolerance limits for the pulsatility index and the resistivity index on the right side were smaller compared to the limits on the left side (Table 3).

The average interhemispheric index calculated on the basis of uncorrected velocity values for the MCA was 1.03, whereas the interval for left and right limits of tolerance was 0.38 to 1.75 (Table 3). Mean velocity on the left side as high as 75% of the velocity on the right side is considered...
“normal,” whereas on the right side velocity as high as 62% of the velocity on the left side is still “normal.” The respective values for angle-corrected velocity values were similar (Table 3). The tolerance intervals for other arteries were wider, particularly for the angle-corrected velocities.

The average left-to-right interhemispheric ratios in impedance indexes were close to 1.0 for uncorrected and angle-corrected values (Table 3). However, the width of the tolerance interval for the left-to-right ratios in the resistivity index in the MCA varied from 0.68 to 1.31 for uncorrected values and from 0.54 to 1.62 for angle-corrected values, respectively (Table 3). For other arteries, the tolerance was, in general, much wider, and it also was wider for angle-corrected resistivity index and pulsatility index values. No

### Table 2. Pearson Correlations Coefficients ($r$) for Ultrasound Doppler Parameters From Right Arteries With Corresponding Parameters From Left Arteries in 57 Children With Sickle Cell Disease

<table>
<thead>
<tr>
<th>Artery</th>
<th>Parameter</th>
<th>Blood Flow Doppler Parameters Uncorrected for the Angle of Insonation</th>
<th>Blood Flow Doppler Parameters Corrected for the Angle of Insonation</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Correlation Coefficient</td>
<td>$P$</td>
</tr>
<tr>
<td>MCA</td>
<td>$V_{PS}$</td>
<td>0.43</td>
<td>0.001</td>
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<tr>
<td></td>
<td>$V_{ED}$</td>
<td>0.30</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>$V_{MN}$</td>
<td>0.44</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>RI</td>
<td>0.68</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>PI</td>
<td>0.65</td>
<td>0.000</td>
</tr>
<tr>
<td>ACA</td>
<td>$V_{PS}$</td>
<td>0.54</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$V_{ED}$</td>
<td>0.59</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$V_{MN}$</td>
<td>0.54</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>RI</td>
<td>0.52</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>PI</td>
<td>0.57</td>
<td>0.000</td>
</tr>
<tr>
<td>tICA</td>
<td>$V_{PS}$</td>
<td>0.57</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$V_{ED}$</td>
<td>0.59</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$V_{MN}$</td>
<td>0.54</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>RI</td>
<td>0.43</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>PI</td>
<td>0.50</td>
<td>0.000</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; MCA, middle cerebral artery; PI, pulsatility index; RI, resistivity index; tICA, terminal internal carotid; $V_{ED}$, end-diastolic blood flow velocity; $V_{MN}$, mean blood flow velocity; $V_{PS}$, peak systolic blood flow velocity.

### Table 3. Mean Values of Interhemispheric Differences [Left (L) Values Minus Right (R) Values] and Ratios (L Values Divided by R Values) of Peak-Systolic, Mean and End-Diastolic Velocities, With Their Gaussian Tolerance Intervals (in Parentheses), in the Middle Cerebral (MCA), Anterior Cerebral (ACA) and Terminal Segments of Internal Carotid (tICA) Arteries Obtained With Imaging Transcranial Color-Coded Duplex Sonography (TCCS) With and Without Correction of Angle of Insonation in 57 Children With Sickle Cell Disease

<table>
<thead>
<tr>
<th>Artery</th>
<th>Variables</th>
<th>MCA</th>
<th>L–R</th>
<th>L/R</th>
<th>ACA</th>
<th>L–R</th>
<th>L/R</th>
<th>tICA</th>
<th>L–R</th>
<th>L/R</th>
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<td>Uncorrected</td>
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<td></td>
<td>$V_{PS}$</td>
<td>0.47 (–106; 106)</td>
<td>1.02 (0.27; 3.6; 1.98)</td>
<td>7.55 (–118; 130)</td>
<td>1.15 (0.46; 2.81)</td>
<td>2.46 (–103; 107)</td>
<td>1.06 (0.63; 2.21)</td>
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<td></td>
<td>$V_{MN}$</td>
<td>1.33 (–72; 75)</td>
<td>1.03 (0.26; 3.8; 1.75)</td>
<td>5.38 (–81; 91)</td>
<td>1.14 (0.45; 2.89)</td>
<td>3.33 (–73; 78)</td>
<td>1.08 (0.56; 2.23)</td>
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<tr>
<td></td>
<td>$V_{ED}$</td>
<td>5.29 (–59; 69)</td>
<td>1.6 (0.3; 2.1)</td>
<td>4.24 (–50; 58)</td>
<td>1.15 (0.43; 3.34)</td>
<td>5.22 (–44; 54)</td>
<td>1.12 (0.60; 2.43)</td>
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<td></td>
<td>RI</td>
<td>–0.01 (–0.14; 0.13)</td>
<td>0.99 (0.01; 0.68; 1.31)</td>
<td>0.00 (–0.08; 0.17; 0.17)</td>
<td>1.01 (0.66; 1.43)</td>
<td>–0.03 (–0.22; 0.16)</td>
<td>0.96 (0.06; 1.55)</td>
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<tr>
<td></td>
<td>PI</td>
<td>–0.02 (–0.32; 0.28)</td>
<td>0.99 (0.17; 0.52; 1.44)</td>
<td>0.00 (–0.06; 0.37)</td>
<td>1.02 (0.60; 1.78)</td>
<td>–0.05 (–0.45; 0.35)</td>
<td>0.96 (0.30; 1.88)</td>
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<tr>
<td></td>
<td>Angle-corrected</td>
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<td></td>
<td>$V_{PS}$</td>
<td>–4.34 (–80; 73)</td>
<td>0.99 (0.22; 0.29; 1.69)</td>
<td>6.36 (–74; 87)</td>
<td>1.15 (0.42; 2.92)</td>
<td>4.37 (–79; 87)</td>
<td>1.07 (0.63; 2.64)</td>
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<tr>
<td></td>
<td>$V_{MN}$</td>
<td>–2.24 (–56; 53)</td>
<td>1.0 (0.23; 0.31; 1.84)</td>
<td>4.24 (–49; 57)</td>
<td>1.14 (0.48; 2.99)</td>
<td>5.26 (–55; 64)</td>
<td>1.13 (0.61; 2.56)</td>
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<tr>
<td></td>
<td>$V_{ED}$</td>
<td>3.23 (–50; 55)</td>
<td>1.2 (0.78; 2.5; 5.51)</td>
<td>3.15 (–31; 38)</td>
<td>1.15 (0.54; 3.46)</td>
<td>5.23 (–40; 50)</td>
<td>1.16 (0.45; 2.66)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>RI</td>
<td>–0.01 (–0.24; 0.21)</td>
<td>0.99 (0.23; 0.54; 1.62)</td>
<td>0.00 (–0.09; 0.21; 0.22)</td>
<td>1.03 (0.49; 1.74)</td>
<td>–0.02 (–0.10; 0.14)</td>
<td>0.99 (0.02; 0.52; 2.27)</td>
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<tr>
<td></td>
<td>PI</td>
<td>–0.02 (–0.38; 0.32)</td>
<td>0.98 (0.24; 0.53; 1.68)</td>
<td>0.01 (–0.06; 0.36)</td>
<td>1.05 (0.43; 2.04)</td>
<td>–0.04 (–0.18; 0.05)</td>
<td>0.99 (0.33; 0.44; 2.60)</td>
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</table>

ACA indicates anterior cerebral artery; L, left; MCA, middle cerebral artery; PI, pulsatility index; R, right; RI, resistivity index; tICA, terminal internal carotid; $V_{ED}$, end-diastolic blood flow velocity; $V_{MN}$, mean blood flow velocity; $V_{PS}$, peak systolic blood flow velocity.

Differences given in cm/s, otherwise no units. L values minus R values and ratios (L values divided by R values) of peak systolic, mean, and end-diastolic velocities, with their Gaussian tolerance intervals (in parentheses).
significant association of between-sides differences or ratios and Doppler parameter regarding age and gender after adjustment for hematocrit level and hemoglobin concentration was found for any artery.

Discussion

Our study provides tolerance limits for interhemispheric differences in transcranial color-coded duplex sonography parameters for children with SCD without arterial stenosis. We believe that interhemispheric differences within these limits in a child in whom TCD velocities are \(<170\) cm/s likely do not represent arterial stenosis, whereas the differences beyond the tolerance limits may indicate the presence of stenosis. The latter suggestion needs to be verified in a separate study in a group of children with and without stenosis. These limits also may help distinguish stenosis from hyperemia in children with TCD velocities \(>170\) cm/s, a concept that deserves further study. Tolerance limits, therefore, may allow more reliable selection of children who would benefit most from close TCD or MRA surveillance and treatment.\(^{16,17}\)

Average side-to-side differences in hemodynamic parameters in adults were reported to be negligible, and thus substantial interhemispheric asymmetry is commonly interpreted as a sign of arterial narrowing.\(^{2,9,18–20}\) The statistical average group difference cannot be applied to an individual in whom the exact configuration of the circle of Willis,\(^{21}\) including presence, caliber, and course of each artery,\(^{22,23}\) as well as the degree of interhemispheric anatomic,\(^{24–26}\) physiological,\(^{27–29}\) and pathophysiological differences, is a priori unknown.\(^{18,23,30,31}\) Large variability in side-to-side impedance indexes, modest correlation coefficients for vessels that supposedly have no stenosis, and hemispheres with the same circulating oxygen content and hemoglobin indicate that there is not such a tight agreement between sides in blood flow redistributions in response to chronic oxygen deficit.\(^{6–8,30}\)

Also, a minor arterial narrowing, which could have remained undetected on MRA, potentially contributed to the variability in our study because analysis of the Hagen-Poiseuille equation indicates that even small changes in artery radius may result in extremely drastic changes in flow velocity. Assuming that \(140\) cm/s is an average MCA velocity in asymptomatic children with SCD, 10% reduction of mean MCA radius of 1.5 mm should increase the velocity to \(213\) cm/s to maintain the same blood flow, whereas the 25% reduction should increase the velocity to \(442\) cm/s. In the STOP II trial, children with TCD velocity \(>200\) cm/s but without moderate MRA narrowing, defined as \(>25\%\) diameter reduction, were classified as having hyperemia.\(^2\) Such minor to moderate narrowing, however, may have important significance in children with SCD in whom adaptation to altered blood rheology may not be well-balanced. Hence, the diagnostic importance of the reference tolerance limits of interhemispheric differences of those blood flow Doppler parameters that are commonly used in screening children with SCD.

The use of side-to-side indices to detect stenosis can be beneficial because they are supposed to be resistant to bilateral physiological changes.\(^{32}\) The use of interhemispheric indices improves interobserver and intra-observer reproducibility of Doppler parameters by \(\approx 50\%\).\(^{32}\) A strong association between asymmetrical MCA velocity pattern, taken as 15% side-to-side variations in healthy adults.\(^{19,20}\) and hemodynamically significant carotid disease or presence of underlying ischemic stroke was reported.\(^{18}\) Higher flow velocity asymmetry was reported in healthy white children, which was almost similar to asymmetry observed in our group.\(^{10}\) The threshold of 15% of interhemispheric differences as a reference tolerance limit, therefore, should no longer be applied to the individual child with SCD for differentiation of hyperemia from arterial stenosis.

We believe that uncorrected transcranial color-coded duplex sonography velocities can be useful for interpretation of conventional TCD data with some minor reservations, however, because they are not necessarily the same.\(^{33,34}\) We applied our tolerance limit of 75 cm/s for interhemispheric differences in uncorrected mean MCA velocities to TCD data published by Adams et al\(^3\) on TCD detection of arterial stenoses in patients with SCD. Twelve out of 13 stenoses could have detected using the limit, which itself can be a sensitive marker to discriminate hyperemia from stenosis. This hypothesis, however, needs to be verified in future studies.

The commonly used term “hyperemia” needs clarification in regard to children with SCD, in whom hyperemic blood flow velocity and shear rate adapt to increased blood viscosity. Differentiation of such hyperemic flow from pathological hyperemia is a matter of arbitrary judgment. We define the latter as blood flow velocity in a particular artery exceeding 170 cm/s without presence of narrowing.

Our number of subjects is relatively small compared to studied groups of healthy children. The National Committee for Clinical Laboratory Standards recommends that the sample size should consist of at least 120 values.\(^{35,36}\) The Committee recognizes, however, that in a special category of individuals, 39 observations is the required minimum to compute a 95% reference interval at 2.5% and 97.5% points of the distribution.

Conclusion

Our study provides tolerance limits for inter-hemispheric differences in TCCS parameters for children with SCD. The limits can be helpful in identification of intracranial arterial narrowings of children undergoing ultrasound screening for primary stroke prevention.

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Disclosures

None.

References


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