Transcranial Doppler Correlation With Cerebral Angiography in Sickle Cell Disease

Robert J. Adams, MD; Fenwick T. Nichols, MD; Ramon Figueroa, MD; Virgil McKie, MD; and Thomas Lott, MD

Background and Purpose: Cerebral infarction in sickle cell disease is associated with arterial narrowing or occlusions of intracranial arteries. Primary stroke prevention would be feasible if a noninvasive screening test could be developed to detect intracranial disease in patients before symptoms develop.

Methods: To determine the sensitivity and specificity of transcranial Doppler in detecting significant (>50% lumen diameter reduction) intracranial arterial lesions, we compared transcranial Doppler and cerebral angiography in a primarily young, symptomatic group of 33 patients (18 males and 15 females) with sickle cell disease.

Results: From a total of 34 examinations, transcranial Doppler detected significant abnormalities in 26 of 29 (sensitivity 90%, specificity 100%). Five were normal by both techniques. The transorbital examination detected abnormalities in two patients whose studies were otherwise unremarkable.

Conclusions: Transcranial Doppler is sensitive and specific for the detection of arterial vasculopathy of sickle cell disease. Screening should include a transorbital examination of the distal internal carotid artery as well as examination using the transtemporal approach. (Stroke 1992;23:1073-1077)

KEY WORDS • cerebral infarction • child • anemia, sickle cell • ultrasonics

Transcranial Doppler (TCD) can detect intracranial arterial stenosis caused by vasospasm after subarachnoid hemorrhage,1 atherosclerosis,2,3 and the arterial vasculopathy associated with sickle cell disease (Hb SS).4 Some patients with homozygous Hb SS develop intimal lesions at characteristic arterial sites, specifically, the distal internal carotid artery (ICA) and the proximal segments of the middle cerebral artery (MCA) and anterior cerebral artery (ACA).4,5,6 These lesions may produce stenosis or occlusion that results in cerebral infarction.

Stroke is an important complication that occurs in at least 5% of Hb SS patients, mostly children.7,8 While regular blood transfusion prevents recurrent stroke in Hb SS,9,10 primary stroke prevention has not been feasible because the patients at highest risk could not be identified before the development of symptoms. If TCD reliably detects the intimal lesions previously seen only on angiography11 or at autopsy,12 screening asymptomatic patients could identify those at highest risk before cerebral infarction occurs.

Transcranial Doppler measures flow velocity in intracranial arteries. Stenosis is detected on the basis of elevated flow velocity in the narrowed arterial segment.13 Velocity criteria for the diagnosis of stenotic lesions have been reported for vasospasm14 and intracranial atherosclerosis3 by comparison with cerebral angiography. Correlation of TCD with angiography in Hb SS has been limited.15 We compared TCD findings in Hb SS patients receiving both studies to determine whether TCD could identify patients with significant intracranial occlusive disease and to examine how well TCD predicted the specific location of arterial lesions.

Subjects and Methods

All but two of the 33 patients (18 males and 15 females) in this series were in either the pediatric or the adult sickle cell disease program of the Medical College of Georgia (Augusta) at the time of their stroke; the other two underwent initial stroke evaluation, including angiography, elsewhere, but were referred for further treatment within 1 year after stroke. The series included all patients with homozygous Hb SS evaluated with cerebral angiography at our institution from June 1986 (when we began performing TCD) through December 1991, plus the two outside patients mentioned above. Most were children, with a mean±SD age of 12±6 (range, 2–30) years at the time of angiography. Two patients were evaluated for intracranial hemorrhage, 29 for symptoms of cerebral ischemia, and two for abnormal TCD.

Angiography was usually performed for symptoms of suspected cerebral ischemia or proven intracranial hemorrhage. Two asymptomatic patients underwent angiography because of abnormal TCD. One asymptomatic patient had two sets of studies separated by 4 years. The patients received hydration and reduction of Hb SS to 30% or less of total hemoglobin before angiography.

From the Departments of Neurology (R.J.A., F.T.N.), Radiology (R.F., T.L.), and Pediatrics (V.M.), Medical College of Georgia, Augusta.

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Address for correspondence: Robert J. Adams, MD, Department of Neurology, HB-2060, Medical College of Georgia, Augusta, GA 30912.

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Technical aspects of the TCD examination were the same as those reported elsewhere,17 with one exception: all the patients were anemic (mean±SD hematocrit, 24±4%), which caused a generalized increase in velocities of 40% above what would be expected based on the age of these patients.18

The TCD examinations were performed at or near the time of angiography. No patients were sedated for TCD. Our technique evolved over the 5 years of the study. Patients examined early in the study typically did not have the posterior cerebral artery (PCA) velocity recorded nor did they undergo transorbital examination of the ICAs. Most patients studied within the last 2 years had transorbital examination and PCA measurements. In 31 cases, TCD and angiography were performed within 2 months of each other. We also included data from two other patients who had been clinically unchanged since angiography performed 10 and 11 months before TCD. A single representative velocity waveform was used with low molecular weight ionic contrast material (Hexabrix-320, Mallinckrodt Medical, Inc., St. Louis, Mo.). Contrast load was 2 cc/kg body weight or less.

In Table 1, the TCD findings of high velocity leading to an abnormal classification are described with their corresponding angiographic abnormalities. Eighteen patients had one or more arterial mean velocities exceeding 190 cm/sec. The qualifying high velocities in this group ranged from 200 to 280 cm/sec, with a mean of 234±24 cm/sec. Ten of 18 patients had both transorbital and transtemporal examinations. Five transorbital ICA measurements exceeded 190 cm/sec; in two of these, the corresponding transtemporal velocity estimates were unremarkable. Two patients had high-velocity signals flowing toward the probe from the transorbital approach that were coded as ICA. Both were found to have ICA occlusion and ipsilateral posterior–anterior collateral flow through the posterior communicating artery that was assumed to be the source of the high-velocity signal.

Four patients had asymmetric studies, with either low MCA or high ACA velocity relative to ipsilateral MCA velocity (Table 2). Low MCA velocity accompanied ICA occlusion (case 19) and severe MCA stenosis (case 22) with leptomeningeal collateral to MCA branches. In case 20, severe bilateral ICA disease caused both MCA velocities to be low (normal ratio); stenosis was detected by a high ACA/MCA ratio. The patient in case 21 had the least remarkable angiogram, showing only left ACA stenosis that was detected by a high right ACA/MCA ratio. Collateral flow from the right ACA to both postcommunicating ACA segments was the probable cause of velocity elevation.

In four studies, the operator could not identify an MCA signal at depths of 45±5 mm despite demonstration of an ultrasound window on that side. Three patients had unilateral and one had bilateral ICA occlusion. Review of the angiographic series showed delayed filling of the proximal MCA on the side of a large infarct in one patient, no visualization in two other patients with large infarcts, and complete restitution of MCA territory flow solely from leptomeningeal collaterals without clear evidence of proximal MCA filling in the fourth patient.
TABLE 1. Correlation of High-Velocity Transcranial Doppler Findings With Angiographic Findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Transcranial Doppler ultrasonography (cm/sec mean velocity)</th>
<th>Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L MCA=200 (R MCA=110)</td>
<td>L MCA stenosis 50–75%</td>
</tr>
<tr>
<td></td>
<td>R ACA=210</td>
<td>R ACA stenosis 75–99%</td>
</tr>
<tr>
<td>2</td>
<td>R MCA=240</td>
<td>B ICA stenosis 50–75% (R)</td>
</tr>
<tr>
<td></td>
<td>L MCA=260</td>
<td>75–99% (L)</td>
</tr>
<tr>
<td>3</td>
<td>R ICA=250 (L MCA=148)</td>
<td>B ICA stenosis 50–75%</td>
</tr>
<tr>
<td>4</td>
<td>L ICA=200 (R MCA=120)</td>
<td>L ICA stenosis 50–75%</td>
</tr>
<tr>
<td>5</td>
<td>R MCA=280 (L MCA=190)</td>
<td>R MCA stenosis 75–99%</td>
</tr>
<tr>
<td>6</td>
<td>L MCA=240 (R MCA=190)</td>
<td>L ICA stenosis 75–99%</td>
</tr>
<tr>
<td>7</td>
<td>L MCA=220 (R MCA=100)</td>
<td>L MCA stenosis 50–75%</td>
</tr>
<tr>
<td>8</td>
<td>R ICA=260 (L MCA=70)</td>
<td>R ICA stenosis 75–99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L ICA occlusion</td>
</tr>
<tr>
<td>9</td>
<td>R ACA=220 (L ACA=90)</td>
<td>R ACA stenosis 75–99%</td>
</tr>
<tr>
<td>10</td>
<td>L ICA=263</td>
<td>B ICA stenosis 50–75% (L)</td>
</tr>
<tr>
<td></td>
<td>R ICA=267</td>
<td>25–50% (R)</td>
</tr>
<tr>
<td>11</td>
<td>L ICA=215 (R MCA=151)</td>
<td>L ICA occlusion, large L PCoA</td>
</tr>
<tr>
<td>12</td>
<td>R MCA=245 (L MCA=160)</td>
<td>R MCA stenosis 50–75%</td>
</tr>
<tr>
<td>13</td>
<td>L MCA=200 (R MCA=74)</td>
<td>L ICA stenosis 75–99%</td>
</tr>
<tr>
<td>14</td>
<td>L ICA=216 (R MCA=105)</td>
<td>L ICA stenosis 50–75%</td>
</tr>
<tr>
<td>15</td>
<td>L MCA=240 (R MCA=117)</td>
<td>L MCA stenosis 50–75%</td>
</tr>
<tr>
<td>16</td>
<td>R MCA=220 (L MCA=111)</td>
<td>R MCA stenosis 75–99%</td>
</tr>
<tr>
<td></td>
<td>L ACA=260 (R ACA=65)</td>
<td>L ACA stenosis 75–99%</td>
</tr>
<tr>
<td>17</td>
<td>L ICA=215</td>
<td>L ICA occlusion, large L PCoA</td>
</tr>
<tr>
<td>18</td>
<td>R ICA=220</td>
<td>R ICA stenosis 50–75%</td>
</tr>
<tr>
<td>19</td>
<td>L MCA=257</td>
<td>L MCA stenosis 50–75%</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent contralateral velocity for comparison. L, left; R, right; B, bilateral; MCA, middle cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery (intracranial segment unless noted); PCoA, posterior communicating artery.

There were three false-negatives. One patient had bilateral ICA narrowing just distal to the origin of the ophthalmic arteries but normal M-1 segments. (Transorbital ICA examination was not performed in this early case.) Another patient had bilateral suprachinoid ICA occlusions, and his anterior circulation was filled from a

<table>
<thead>
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<th>Angiography</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Asym: Low L MCA velocity (0.37)</td>
<td>L ICA occlusion</td>
<td>C/W and LM collaterals</td>
</tr>
<tr>
<td>20</td>
<td>Asym: R ACA &gt;&gt; MCA (1.4)</td>
<td>R ICA stenosis 75–99%</td>
<td>C/W and LM collaterals</td>
</tr>
<tr>
<td>21</td>
<td>Asym: R ACA &gt;&gt; MCA (1.9)</td>
<td>L ACA stenosis 50–75%</td>
<td>R-L flow through ACoA</td>
</tr>
<tr>
<td>22</td>
<td>Asym: Low L MCA velocity (0.45)</td>
<td>L MCA stenosis</td>
<td>Repeat of case #7; severe MCA stenosis with LM collaterals</td>
</tr>
<tr>
<td>23</td>
<td>ND: No L MCA</td>
<td>L ICA occlusion</td>
<td>Large infarct, MCA not visualized</td>
</tr>
<tr>
<td>24</td>
<td>ND: No L MCA R ACA &gt;&gt; MCA (1.4)</td>
<td>L ICA occlusion</td>
<td>Large infarct, slow MCA filling from C/W</td>
</tr>
<tr>
<td>25</td>
<td>ND: No L or R MCA</td>
<td>B ICA occlusion</td>
<td>LM collaterals only</td>
</tr>
<tr>
<td>26</td>
<td>ND: No R MCA</td>
<td>R ICA occlusion</td>
<td>Large infarct, MCA not visualized</td>
</tr>
<tr>
<td>27</td>
<td>FN: Low R MCA (0.65) (cervical)</td>
<td>R ICA occlusion filling</td>
<td>Large infarct, slow MCA</td>
</tr>
<tr>
<td>28</td>
<td>FN:</td>
<td>B ICA stenosis 75–99%</td>
<td>No transorbital exam</td>
</tr>
<tr>
<td>29</td>
<td>FN: (Basilar velocity high)</td>
<td>B ICA occlusion</td>
<td>Large PCoAs without high velocity flow</td>
</tr>
</tbody>
</table>

Asym, asymmetrical; ND, not detected; FN, false-negative; L, left; R, right; B, bilateral; MCA, middle cerebral artery; ICA, internal carotid artery; ACA, anterior cerebral artery; ACoA, anterior communicating artery; PCoA, posterior communicating artery; C/W, circle of Willis; LM, leptomeningeal collaterals.
very large right posterior communicating artery through the
right ICA, with cross-filling to the left by the anterior
communicating artery. This patient had the
highest basilar artery velocity recorded in this series
(143 cm/sec, with the mean ± SD basilar velocity for this
series being 83 ± 28 cm/sec), but basilar artery velocities
were not considered in the TCD classification.

In cases with unilateral high velocity, the opposite
MCA or ACA reading where available is also shown in
Table 1 for comparison. Two patients (cases 5 and 6)
had velocities of 190 cm/sec opposite stenotic lesions but
did not have significant ICA narrowing. In both pa-
tients, the ACA on the side opposite the stenosis fed
both A2 segments, and in one (case 6) there was also
mild narrowing (25–50%) of the terminal ICA on the
side opposite the major stenotic lesion.

There were no complications from angiographic ex-
amination. As expected, ICA disease was common, with
20 patients showing ICA involvement, typically in the
distal segment just beyond the origin of the ophthalmic
artery. Seven patients had bilateral ICA disease. One
19-year-old female had a stenotic lesion in the cervical
ICA at its origin, but the remainder of the lesions were
intracranial. Eight of 29 had MCA and five ACA
stenosis. No vertebral, basilar, or PCA lesions were
noted.

Of the 18 cases classified as abnormal based on high
velocity, the correct arterial segment was identified by
TCD in 14. The four identification errors were two ICA
stenoses read as MCA lesions and two posterior com-
 municators initially identified as ICA lesions.

Discussion

The results of our study indicate that TCD is sensitive
and specific in the identification of Hb SS patients with
intracranial occlusive vasculopathy. Most stenotic le-
sions were correctly identified on the basis of high flow
velocity. Our findings suggest that for patients with Hb
SS, TCD is an effective screening test to select those
with significant arterial stenosis.

The selection of TCD criteria of abnormality was
based on previous work comparing TCD velocities in
nonanemic children,19 with those from neurologically
asymptomatic Hb SS patients18 and from the correlation
of TCD velocity with angiographically documented ar-
terial lesions.15 The cutoff of 190 cm/sec represented the
lowest mean velocity seen in a stenotic arterial segment
in our earlier study.15 It also represents the 98th per-
centile of MCA mean velocities from a series of 200
neurologically asymptomatic Hb SS patients undergoing
TCD screening at our institution. In children with Hb
SS, the MCA velocity is typically 100–130 cm/sec.18

The determination of a significant MCA asymmetry is
arbitrary. However, MCA velocities in normal individ-
uals and elderly patients without intracranial arterial
lesions by TCD usually do not vary more than 10–15%
from side to side.20,21 The ACA is usually 80% or less of
the velocity of the MCA and exceeds 120% of the MCA
velocity in the presence of either intracranial or extra-
cranial pathology.20 The criteria used in the present
study were conservative.

The derivation of cerebral vessel occlusion by TCD must be
made with caution and requires the demonstration of an
ultrasound window by the recording of other arterial
waveforms on the side in question.17 In one case, we
could record no signals on one side and considered this
a technical failure due to poor ultrasound transmission.
The ultrasound window is generous in patients of this
age, and we have come to regard the inability to detect
and follow the MCA signal from depths of 55 to 35 mm
(from the temporal window) as highly suspicious for
abnormality. Not all cases of MCA nondetection repres-
ent MCA occlusion. Review of the full angiographic
series showed no MCA visualization in some cases with
extensive ipsilateral infarction; slow, delayed filling
from Willisian collaterals; or reconstitution from lepto-
meningeal but not Willisian sources, presumably pro-
ducing little if any orthograde flow through the proximal
MCA.

The study highlighted several problems. Early on,
studies were often incomplete and did not include
transorbital examination, which requires relatively more
operator skill and subject compliance than does trans-
 temporal examination. The precise arterial segments
examined are not known, but it is assumed that the flow
toward the probe is from the carotid siphon at or near
the origin of the ophthalmic artery and flow away from
the probe represents the more distal ICA segments. The
transorbital and transtemporal examinations presum-
ably do not examine the same arterial segments, but
there may be overlap in some cases. Reversal of oph-
thalmic flow direction, used as an indicator of disease in
some conditions, is not encountered in this disease
because lesions are distal to the origin of this vessel.
Although more difficult to perform, the transorbital
examination is important for screening patients with Hb
SS.

The TCD examination in children with Hb SS is
complicated technically by several factors. Flow veloc-
ities are generally high because of their young age and
the significant anemia that increases cerebral blood
flow.22 Distances between the arterial segments are
small relative to the size of the ultrasound sample
volume. In the presence of major vessel pathology,
Willisian, leptomeningeal, or extracranial–intracranial
collateral pathways may be activated. Acutely, abnor-
mally high velocities may be recorded from vessels
acting as collateral sources, such as a PCA or posterior
communicator, and these findings may support the
diagnosis of occlusion of other vessels. However, the
chronic state may be associated with dilatation of collat-
eral vessels causing lower velocities that may fall within
normal limits. Cerebral infarcts may reduce the cerebral
blood flow demands on one or both sides and could lead
to lower flow velocities even though arterial narrowing
may be present. This series contained two examples of
velocities exceeding 190 cm/sec in the absence of ≥50%
narrowing, probably because of collateral flow effects.

These concerns, however, are largely theoretical be-
cause most patients with severe flow derangements due
to vessel occlusion or infarction will have evident clin-
ical symptoms. In clinical application, it is more impor-
ant that TCD detect moderate-to-severe stenosis in
asymptomatic individuals with Hb SS. Our results indi-
cate that with operator experience and training, TCD is
highly sensitive and specific in detecting Hb SS-related
arterial disease. Prospective screening of asymptomatic
patients has determined that TCD also predicts clinical
stroke in children with Hb SS.23
References


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