Transcranial Doppler Correlation With Cerebral Angiography in Sickle Cell Disease

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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).[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 angiography[11] 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 vasospasm[14] and intracranial atherosclerosis[3] 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 symptomatic 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.

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Biplane, magnification film screen angiography 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.

All angiograms were comprehensively scored for abnormalities in all arterial segments. The scores were rendered independently of the TCD findings. Details of the angiographic findings of most of these patients have been reported elsewhere.[16]

From 1986 to 1988, all TCD examinations were performed with a TC264B device (Eden, Uberlingen, FRG). After 1988, a TC2000 (Eden) device was used. 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, expressed as the time-averaged mean, was recorded for each artery if available. The TCD examinations were not blinded, although most were performed before angiography.

From the transtemporal approach, we did not routinely distinguish the distal ICA from the proximal MCA because 1) the sample volume of the TCD likely includes both segments at certain depth settings; and 2) there are no unambiguous vascular landmarks without compression testing, which was considered undesirable in this setting.

When doing the transorbital examination, the operator generally placed the probe at about a 10–20° angle off of sagittal pointing toward midline, with the transducer just above the orbit. The ophthalmic artery was usually encountered at 45–50-mm depth and demonstrated a more pulsatile waveform than the ICA. Flow with the appropriate "internal," low-pulsatility waveform appearance between 60 and 70 mm was coded as the ICA. A high-velocity posterior communicating artery with flow toward the probe could be mistaken as ICA stenosis, but risk of error was considered acceptable because high velocity in either case would represent severe disease.

A patient was labeled true positive if the angiogram showed one or more stenotic areas of at least 50% or greater lumen diameter reduction in either the extracranial or intracranial ICA or the MCA, ACA, PCA, or basilar arteries. A true negative indicated the absence of these findings.

A patient was considered TCD positive if one or more of the following criteria were present: 1) a mean velocity of 190 cm/sec or greater in any artery, 2) abnormally low velocity in the MCA defined as MV<70 cm/sec and an MCA ratio (lower/higher) of 0.5 or less, 3) an ACA/MCA ratio of ≥1.2 on the same side, or 4) the inability to record an MCA in the presence of a demonstrated ultrasound window. Pulsatility index was not considered.

Sensitivity and specificity were computed from standard formulas. TCD was given credit in the identification of a patient as positive even if the abnormal arterial segment was not correctly identified by the operator (e.g., a high MCA velocity by TCD may have been due to a distal ICA stenosis on angiography). We considered this appropriate because a screening test need only identify which patients require further study and because ICA and MCA stenoses were assumed to have the same clinical significance in Hb SS.

Results

The 33 Hb SS patients in the present study underwent 34 TCD and cerebral angiography examinations during the 5-year review period. Angiography revealed significant disease in 29 of 34 studies. The TCD findings were abnormal in 26 of 29. There were three false-negatives and no false-positives. Sensitivity was 90%, and specificity was 100%.

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 communicator 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 post communicating 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

Case	Transcranial Doppler ultrasonography (cm/sec mean velocity)	Angiography
1	L MCA=200 (R MCA=110)	L MCA stenosis 50–75%
	R ACA=210	R ACA stenosis 75–99%
2	R MCA=240	B ICA stenosis 50–75% (R)
	L MCA=260	75–99% (L)
3	R ICA=250 (L MCA=148)	B ICA stenosis 50–75%
4	L ICA=200 (R MCA=120)	L ICA stenosis 50–75%
5	R MCA=280 (L MCA=190)	R MCA stenosis 75–99%
6	L MCA=240 (R MCA=190)	L ICA stenosis 75–99%
7	L MCA=220 (R MCA=100)	L MCA stenosis 50–75%
8	R ICA=260 (L MCA=70)	R ICA stenosis 75–99%
		L ICA occlusion
9	R ACA=220 (L ACA=90)	R ACA stenosis 75–99%
10	L ICA=263	B ICA stenosis 50–75% (L)
	R ICA=267	25–50% (R)
11	L ICA=215 (R MCA=151)	L ICA occlusion, large L PCoA
12	R MCA=245 (L MCA=166)	R MCA stenosis 50–75%
13	L MCA=200 (R MCA=74)	L ICA stenosis 75–99%
14	L ICA=216 (R MCA=105)	L ICA stenosis 50–75%
15	L MCA=240 (R MCA=117)	L MCA stenosis 50–75%
16	R MCA=220 (L MCA=111)	R MCA stenosis 75–99%
	L ACA=260 (R ACA=65)	L ACA stenosis 75–99%
17	L ICA=215	L ICA occlusion, large L PCoA
18	R ICA=220	R ICA stenosis 50–75%
	L MCA=257	L MCA stenosis 50–75%

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 supraclinoid ICA occlusions, and his anterior circulation was filled from a

TABLE 2. Correlation of Reduced-Velocity Transcranial Doppler Findings With Angiographic Findings

Case	Transcranial Doppler ultrasonography	Angiography	Comments
19	Asym: Low L MCA velocity (0.37)	L ICA occlusion	C/W and LM collaterals
20	Asym: R ACA >>MCA (1.4)	R ICA stenosis 75–99%	C/W and LM collaterals
	B MCA <70	L ICA occlusion	
21	Asym: R ACA >>MCA (1.9)	L ACA stenosis 50–75%	R-L flow through ACoA
22	Asym: Low L MCA velocity (0.45)	L MCA stenosis	Repeat of case #7; severe MCA stenosis with LM collaterals
23	ND: No L MCA	L ICA occlusion	Large infarct, MCA not visualized
24	ND: No L MCA R ACA>MCA (1.4)	L ICA occlusion	Large infarct, slow MCA filling from C/W
25	ND: No L or R MCA	B ICA occlusion	LM collaterals only
26	ND: No R MCA	R ICA occlusion	Large infarct, MCA not visualized
27	FN: Low R MCA (0.65) (cervical)	R ICA occlusion filling	Large infarct, slow MCA
28	FN:	B ICA stenosis 75–99%	No transorbital exam
29	FN: (Basilar velocity high)	B ICA occlusion	Large PCoAs without high velocity flow

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 patients, the ACA on the side opposite the stenosis fed both A_2 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 examination. 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 communicators 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 lesions 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 patients[18] and from the correlation of TCD velocity with angiographically documented arterial 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 percentile 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 individuals 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 extracranial pathology.[20] The criteria used in the present study were conservative.

The diagnosis of 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 represent 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 leptomeningeal but not Willisian sources, presumably producing 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 transtemporal 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 presumably do not examine the same arterial segments, but there may be overlap in some cases. Reversal of ophthalmic 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 velocities 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, abnormally 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 dilation of collateral 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 because most patients with severe flow derangements due to vessel occlusion or infarction will have evident clinical symptoms. In clinical application, it is more important that TCD detect moderate-to-severe stenosis in asymptomatic individuals with Hb SS. Our results indicate 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]

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