Cerebral Arteriovenous Malformations: Diagnostic Value of Echo-Enhanced Transcranial Doppler Sonography Compared with Angiography

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BACKGROUND AND PURPOSE: **The purpose of our study was to examine the clinical value of echo-enhanced transcranial power Doppler sonography (EE-TCD), including it ability to assess hemodynamic parameters of the intracranial vasculature, in patients with suspected cerebral arteriovenous malformations (AVMs) and to compare this method with angiography.**

METHODS: **Sixteen patients with suspected cerebral AVMs were examined with EE-TCD and angiography. As an echo-enhancing agent, SHU 508A (Levovist) was administered intravenously by bolus injection in nine patients and by continuous infusion in seven. Sonograms were reviewed without knowledge of other imaging results and were correlated with angiographic findings.**

RESULTS: **Angiography showed AVMs in 12 of 16 patients. Eleven lesions were located in the anterior or middle fossa and one was in the posterior fossa. EE-TCD was slightly less sensitive in the detection of AVMs (92%, 11/12 lesions), since in one patient the lacking acoustic window did not allow a transcranial examination. EE-TCD slightly underestimated AVM size compared with angiographic findings but showed feeding arteries with sufficient acoustic properties. In seven patients (58%), angiography revealed a coincidental blood supply from another intracranial or extracranial vessel, which was missed by EE-TCD in all cases. Assessment of peak systolic velocities and resistive indexes resulted in a higher (mean, 191.1 cm/s) and a lower (mean, 45.7%) value, respectively, in the feeding arteries as compared with the contralateral arteries (mean, 101.8 cm/s and 55.6%, respectively). Side-to-side differences were significantly higher in patients with AVMs than in those without a malformation. Signal enhancement was markedly longer with continuous infusion (mean, 520 seconds ± 28.2) than with bolus injection (mean, 145 seconds ± 10.5) of the contrast agent.**

CONCLUSION: **In our limited study group, EE-TCD was a sensitive method for the detection of AVMs, and Levovist proved to be a safe and effective echo-enhancing substance.**

According to the literature, in 20% to 30% of patients undergoing transcranial Doppler sonography, insufficient acoustic properties are responsible for inconclusive or nondiagnostic examinations.

Echo enhancement has proved to be useful in a variety of body regions in which sound attenuation is significant and alters diagnostic quality (1–3). Echo-enhancing microbubble suspensions are safe and highly effective not only in the evaluation of the basal cerebral circulation but also in intracranial masses (2, 4–8).

Since transcranial Doppler sonography will increasingly be used in the evaluation of intracerebral hemorrhage, in the detection of arteriosclerotic and embolic disease, and in vascular malformations (9–13), the combined use of this method with echo-enhanced agents may improve the sensitivity and diagnostic accuracy of these examinations.

Our objective was to examine the diagnostic value, including the sensitivity, of echo-enhanced transcranial Doppler sonography (EE-TCD) in the assessment of the hemodynamic parameters of basal intracranial arteries. Sonographic find-

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ings were compared with angiographic results, which are considered the standard of reference.

Methods

Sixteen patients, 11 males and five females, 12 to 75 years old (mean age, 40 years), who were referred for cerebral angiography because of clinical symptoms or CT or MR imaging findings suggestive of arteriovenous malformations (AVMs), underwent EE-TCD within 24 hours before angiography. Patients with AVMs presented with such clinical signs and symptoms as seizures (n = 5), neurologic deficits (n = 3), headache (n = 2), or intracranial hemorrhage (n = 1). One patient was asymptomatic, and diagnosis of AVM was made incidentally.

All EE-TCD examinations were performed by one of three staff radiologists using high-resolution sonographic equipment (HDI 3000, ATL Inc, Bothell, WA) with a 2-MHz sector array. The power mode was considered the color-coded Doppler method of choice in the evaluation of vascular malformations, since it is more sensitive than conventional color Doppler sonography, does not alias, and can depict vessels continuously (14).

In the power Doppler mode, receiver gain was increased until noise appeared, which, however, was not allowed to alter the image. Pulse repetition frequencies were set to a level (500 to 1000 Hz) that allows detection of low-flow states. The dynamic color range was set to 45 to 55 dB. Depths of insonation varied from vessel to vessel, being more superficial in the middle cerebral artery (MCA) (mean, 4.8 cm ± 0.3) than in the anterior cerebral artery (ACA) (mean, 6.3 cm ± 0.3) and the posterior cerebral artery (PCA) (mean, 6.3 ± 0.2) for the ipsilateral approach, respectively.

The average sample volume width for the assessment of spectral Doppler waveforms in the triplex mode was 3 mm. Clear visualization of the vessel over a distance of at least 1 cm was mandatory in order to guarantee correct angle adaptation less than 60° for the assessment of peak systolic velocity (PSV) values in the feeding artery and the respective contralateral vessel. The resistive index (RI) as an angle-independent parameter for vascular resistance [(fmax − fmin)/fmax] in the downstream region was calculated from the spectral waveforms of the Doppler samples.

After obtaining informed consent from the patients, EE-TCD was performed. As an echo-enhancing substance, SHU 508A (Levovist, Schering AG, Berlin, Germany) was administered intravenously. The contrast agent consists of granules of 2.5 or 4.0 g D-galactose microparticles (99.9%) and palmitic acid (0.1%) and has to be shaken for 10 seconds after adding 5 or 7 mL of sterile water, which results in a galactose concentration of 400 mg/mL or 300 mg/mL, respectively. Before being injected, the suspension must be allowed to rest for approximately 2 minutes to obtain an equilibrium and to allow larger bubbles to dissolve. The manufacturer reports that, following this procedure, bubble size is between 2 and 8 μm, with 95% of the particles being smaller than 6 μm, which may sustain multiple transpulmonary passages and recirculations and provides signal enhancement of up to 25 dB in the venous and arterial compartment for a limited time (15).

The agent was administered intravenously via a 19-gauge line either by bolus injection (flow, approximately 0.5 mL/s) in a concentration of 400 mg/mL galactose (volume, 6.5 mL) in nine patients or by continuous infusion (flow rate, 1.3 mL/min) in seven patients with a concentration of 300 mg/mL galactose (volume administered, 8.5 mL). Selection of bolus injection or infusion of the agent was randomized. Continuous infusion was performed with a pump (IVAC P 4000, IVAC Medical Systems, UK) using 50-cm-long connector tubes (Medrad Inc, Pittsburgh, PA). Compared with bolus injection, which usually took 13 seconds, infusion of Levovist lasted 346 seconds. At the end of the infusion, the contrast agent that remained in the connector tube (1 mL) was administered by flushing the tube with saline solution. In all patients undergoing examination with EE-TCD and bolus injection of the Levovist, a minimum of two contrast applications (total volume, 13 mL), one for the investigation of each hemisphere, was necessary. In two patients, contrast administration was performed three times (total volume, 19.5 mL). Comparing this with continuous infusion, only one application of Levovist was used in each of six patients (total volume, 8.5 mL). In each case the contralateral intracranial vessels could be investigated from one side. In one patient, a second infusion of Levovist (total volume, 17 mL) and a transtemporal approach from each side was necessary. Time and quality of echo enhancement after bolus injection or infusion of the agent, as well as hemodynamic measurements, were recorded on videotapes or magnetooptical disks and reviewed independently by one of the investigators not engaged in this particular examination.

Within 24 hours after EE-TCD, cerebral angiography was performed by an interventional radiologist who had no knowledge of the sonographic findings.

For statistical analysis, the Wilcoxon signed-rank test was applied. Because of the limited number of patients and so as not to miss findings with a possible diagnostic relevance, which has to be proved in future investigations with higher patient numbers, *P* values less than .05 were considered statistically significant and *P* values less than. 1 were considered to indicate significance.

TABLE 1: Locations of 12 cerebral arteriovenous malformations shown at angiography and/or MR imaging

Patient	Affected Hemisphere
1	L frontoparietal
2	L parietal
3	R parietooccipital
4	R frontoparietal
5	L parietooccipital
6	R temporooccipital
7	R frontoparietal
8	R insula
9	R parietal
10	Bilateral cerebellar
11	R parietotemporal
12	R parietooccipital

Results

In 16 patients, suspected AVM findings at EE-TCD were compared with angiographic results. Angiography verified lesions in 12 patients and excluded an AVM as the cause of neurologic symptoms in four patients. In one patient with normal angiographic findings, MR imaging revealed a cavernoma in the left temporal lobe. The locations of the 12 lesions found at angiography and MR imaging are listed in Table 1. One lesion (8.3%) was located in the posterior fossa, whereas the other 11 (92%) were found in the anterior or middle fossa.

At angiography, the mean diameter of the AVMs was 3.6 cm ± 1.8; EE-TCD significantly ($P = .05$) underestimated the size of the lesions, showing a mean diameter of 2.8 cm ± 1.8.

Angiography revealed arteries of different vascular distributory regions supplying the nidus in seven (58%) of the 12 AVMs, which could not be assessed with EE-TCD (Table 2).

TABLE 2: Assessment of mean size, arterial supply, and venous drainage of arteriovenous malformations with echo-enhanced transcranial power Doppler sonography (TCD) and angiography

	Mean Size (cm)		Arterial Feeder		Venous Drainage	
Patient	TCD	Angiography	TCD	Angiography	TCD	Angiography
1	2.0	2	L MCA	L MCA	⋯	Deep venous
2	3.3	3	L MCA	L MCA + PCA	⋯	Venous aneurysms
3	3.0	3	R MCA	R MCA	⋯	⋯
4	2.4	3,7	R MCA	R ACA + MCA	Deep venous	Deep venous
5	3.0	2,4	L MCA	L MCA	⋯	⋯
6	⋯	5	⋯	R PCA	Deep venous	Deep venous
7	1.7	2	R MCA	R ACA + MCA	⋯	⋯
8	2.9	2,5	R MCA	R MCA + ACA	⋯	⋯
9	3.3	3,3	R MCA	R PCA bilateral pericallosal	⋯	⋯
10	2.0	4	Bilateral cerebellar	L PICA	⋯	⋯
11	3.0	4	R MCA	R MCA + ACA	⋯	⋯
12	2.5	3,3	R MCA	R MCA + ACA	⋯	⋯

Note.—MCA indicates middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery; PICA, posterior inferior cerebellar artery.

Hemodynamic parameters of the feeding vessels and of the respective vessels on the contralateral side assessed with EE-TCD are listed in Table 3. Peak systolic velocities in the feeding arteries were significantly higher (mean, 191.1 cm/s ± 93.4) than on the contralateral side (mean, 101.8 ± 29.6) at EE-TCD (Fig 1). Also, the RI was lower in the feeders (mean, 45.7% ± 9.5) than in the contralateral vessels (mean, 55.6% ± 5.0).

Differences of peak systolic velocities between the feeding artery and the contralateral vessel ranged from −18.7 cm/s to +184.8 cm/s (mean, 109.2 cm/s ± 89.1) and were significantly higher ($P = .04$) than in the four patients without AVMs (mean, 2.3 cm/s ± 11.3). Similarly, the mean RI differences were significantly higher in AVM patients (mean, −9.8% ± 8.6) than in patients with normal angiographic results (mean, 0.0% ± 3.2).

The duration of echo enhancement after a bolus injection of Levovist ranged from 110 to 188 seconds, with a mean duration 145 seconds ± 10.5. The first pass of the contrast agent resulted in significant blooming artifacts, which could be diminished by reducing receiver gain. TCD signal enhancement lasted significantly longer after infusion of Levovist, with a mean duration of 520 seconds ± 28.2. No color blooming altered the contrast-enhanced images after intravenous infusion, although bubble noise deteriorated the quality of spectral Doppler samples with time.

Discussion

Effectiveness of TCD has been reported not only for the evaluation of basal cerebral arteries and for more peripherally located vessels but also to determine vasomotor reactivity of AVM feeders associated with a steal syndrome and neurologic deficits (16–18). In addition to the increased sensitivity of flow detection and improved spatial resolution of modern sonographic systems, the use of galactose-based contrast agents has significantly improved diagnostic accuracy in various vascular regions (1–3, 6, 7). These intravascular agents contain microbubbles as an effective back-scattering medium, which improves Doppler signal strength in regions with significant sound attenuation.

In our study, EE-TCD had a sensitivity of 92% in the detection of AVMs. In one case (8%) a total sound attenuation at the temporal bone resulted in a nondiagnostic sonographic examination in a patient in whom an AVM was detected angiographically. In all other patients (15/16), EE-TCD examinations were diagnostic. EE-TCD correctly identified the location and the dominant arterial feeder of these lesions but slightly underestimated the size of the malformations as compared with angiographic findings. This might be relevant when planning radiotherapeutic approaches or when assessing changes of the lesion after transluminal embolization therapy. The increased sensitivity of EE-TCD, however, may be of considerable diagnostic importance in the detection of small (≤2.5 cm) AVMs or lesions located in areas difficult to insonate, such as the frontopolar region or the brain stem (12). In our study, all four lesions that were 2.5 cm or smaller were visualized with EE-TCD. The lesion located in the left cerebellar hemisphere was identified correctly with EE-TCD, as were the feeding vessels and the deep venous drainage (Fig 2). The fact that only one lesion (8.3%) was located in the posterior fossa might have selectively influenced the high sensitivity of TCD. Nevertheless, four (30%) of 12 AVMs were smaller than or equal to 2.5 cm. Sensitivity of unenhanced TCD in these small lesions is reported to be highly limited (12). Detection of peripherally located malformations fed by the PCA also remains challenging for EE-TCD. In our study, cerebral angiography revealed feeding vessels emerging from the PCA in three

TABLE 3: Assessment of hemodynamic parameters of the feeding and respective contralateral arteries in echo-enhanced transcranial power Doppler sonography

Patient	Sonographically Located and Evaluated Feeding Artery	Peak Systolic Velocity (cm/s)*		Side-to-Side Differences in PSV	Resistive Index (%)		Side-to-Side Differences in RI
		Right	Left		Right	Left	
1	L MCA	108.0	241.0	+133.0	61	49	−12
2	L MCA	84.2	100.7	+16.5	48	49	+1
3	R MCA	96.2	72.0	+24.2	41	58	−17
4	R MCA	209.3	144.3	+65.0	61	64	−3
5	L MCA	110.9	278.3	+167.4	52	45	−7
6†	…	…	…	…	…	…	…
7	R MCA	130.5	149.2	−18.7	59	58	+1
8	R MCA	253.3	68.5	+184.8	29	55	−26
9	R PCA	391.3	117.3	+274.0	40	55	−15
10	Bilateral cerebellar	109.8	73.7	36.1‡	45	44	1‡
11	R MCA	210.5	95.2	+115.3	35	49	−14
12	R MCA	198.5	68.0	+130.5	50	56	−6

* Assessed in the feeder and in the respective contralateral artery.
† Insufficient acoustic window.
‡ No sign is used in bilateral involvement.
Note.—PSV indicates peak systolic velocity; RI, resistive index.

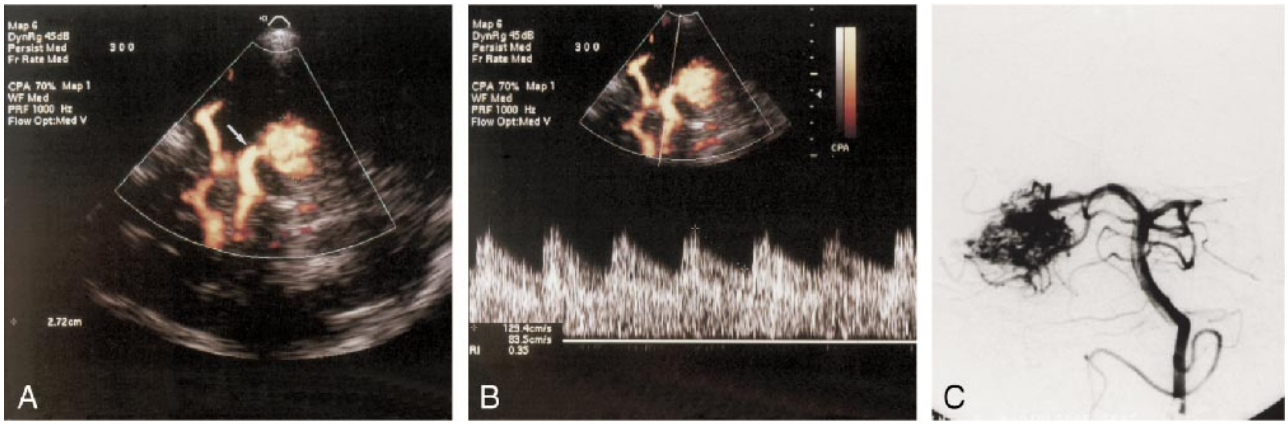

FIG 1. *A,* EE-TCD shows an AVM with a diameter of 2.7 cm. The lesion is fed by the right PCA (*arrow*).
B, In the duplex mode, a high PSV (129.4 cm/s) and a low RI (35%) can be detected, indicating low vascular resistance.
C, Angiogram after catheterization of the left vertebral artery confirms the sonographic diagnosis.

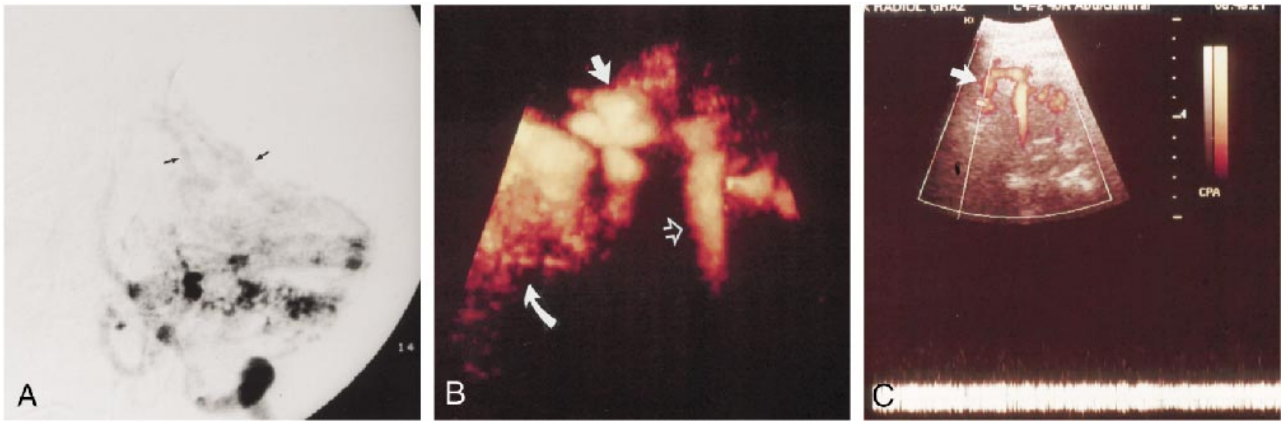

FIG 2. *A,* Medium-sized AVM involving the left cerebellar hemisphere. The lesion gets its arterial supply via the left posterior inferior cerebellar artery (PICA). Large draining veins are exhibited in the early angiographic phase (*arrows*).
B, Three-dimensional image of the lesion depicts the malformation filled with color signals (*curved arrow*). A tortuous and hypertrophic feeder (*straight arrow*), representing the enlarged PICA, emerges from the basilar artery (*open arrow*).
C, Spectral Doppler samples reveal venous flow within a draining vessel adjacent to the PICA (*arrow*).

lesions. EE-TCD assessed two lesions correctly and suggested additional feeders from the MCA. However, EE-TCD did not show the PCA as the source of significant blood supply in these lesions. Possibly, this may have been caused by the subcortical location of the lesions and the inappropriate insonation properties of PCA branches compared with the clear visualization of MCA branches with the transtemporal approach (19).

Hemodynamic parameters of basal intracerebral arteries have been reported in the literature for a large number of healthy adults (19, 20). In our limited study group, we examined the hemodynamic parameters (PSV, RI) of the feeding artery and compared the findings with the values assessed in the same segment of the contralateral vessel. A tendency toward significant side-to-side differences in PSV and RI values was observed in patients with AVMs as compared with patients without AVMs. These findings confirm previously published data from Mast et al (12), who found an inverse correlation of AVM size and peak/mean systolic velocity in the feeding arteries. These findings suggest that a vascular malformation with arteriovenous shunting might be assessed in terms of hemodynamic differences within the basal circulation when the lesion cannot be visualized sonographically. Although PSV values were significantly higher and RI values lower in the lesion's feeding arteries than in the respective contralateral vessel, markedly overlapping values in our small group as well as the possible occurrence of bilateral AVMs make it inadvisable to use side-to-side differences of PSV and RI as diagnostic tools. Furthermore, side-to-side differences of PSV and RI values did not correlate with the size of the lesions, confirming the data reported by Diehl et al (18).

Our EE-TCD examinations showed a high sensitivity for the detection of AVMs and the assessment of hemodynamic parameters in the arterial feeders; however, this technique seems to be limited in its depiction of the entire arterial blood supply and the venous drainage of AVMs, as compared with angiography. Additional feeders visible at angiography in seven patients were entirely missed with EE-TCD. The ability to assess coincidental vascular abnormalities, such as venous and arterial aneurysms, predisposing to clinical symptoms or to hemorrhage, as well as the detection of bilateral blood supply and external-internal collaterals with TCD would be desirable. Marks et al (21) found a significant correlation between peripheral venous drainage and the occurrence of steal symptoms, whereas deep or impaired venous drainage increases the risk of hemorrhage (22, 23). Since a complete evaluation of the complex blood supply and drainage of AVMs, including also external-internal collaterals, is unrealistic with TCD, a confident morphologic evaluation of the involved vessels along with the establishment of cut-off values of PSV, RI, or side-to-side differences is highly questionable.

Levovist is a safe and effective contrast agent, which should be administered by continuous infusion to prolong the echo-enhancing effect and to reduce color-blooming artifacts. Furthermore, infusion of the agent will help to save costs, since the prolonged diagnostic window will allow evaluation of both hemispheres during one examination as compared with bolus injection.

Conclusion

Depending on the location of the lesion, EE-TCD is a sensitive method for the diagnosis, assessment, and localization of AVMs with sufficient acoustic properties. However, compared with angiography, EE-TCD is not capable of depicting accurately the complex arterial blood supply and route of venous drainage or of showing coincidental vascular abnormalities, such as venous aneurysms.

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