AJNR

Echo-Enhanced Transcranial Color-Coded Duplex Sonography in the Diagnosis of Cerebrovascular Events: A Validation Study

A. Kunz, G. Hahn, D. Mucha, A. Müller, K.M. Barrett, R. von Kummer and G. Gahn

AJNR Am J Neuroradiol 2006, 27 (10) 2122-2127
http://www.ajnr.org/content/27/10/2122

ORIGINAL RESEARCH

Echo-Enhanced Transcranial Color-Coded Duplex Sonography in the Diagnosis of Cerebrovascular Events: A Validation Study

A. Kunz
G. Hahn
D. Mucha
A. Müller
K.M. Barrett
R. von Kummer
G. Gahn

BACKGROUND AND PURPOSE: Transcranial color-coded duplex sonography (TCCD) is a diagnostic technique for evaluation of intracranial arteries in patients with acute stroke. Echo-enhancing contrast agents (EEAs) are necessary to visualize intracranial vessels in up to 30% of patients because of limited acoustic bone windows. In this study, we assessed the diagnostic efficacy of echo-enhanced TCCD (eTCCD) in correlation with the gold standard, digital subtraction angiography (DSA).

METHODS: We prospectively evaluated all patients with eTCCD who subsequently underwent DSA for evaluation of cerebrovascular symptoms over a 24-month period. We administered Levovist as an EEA. Two blinded reviewers analyzed all eTCCD findings and correlated them with DSA.

RESULTS: We included 132 consecutive patients (40 women, 92 men; mean age, 58 ± 14 years) with 164 datasets: 24/164 had normal findings, 98/164 had abnormalities of extracranial carotid arteries, 32/164 had abnormalities of intracranial arteries, and 21/164 had abnormalities in vertebrobasilar circulation as determined by DSA. For eTCCD, we found a sensitivity of 82% (95% confidence interval [CI]: 75%–90%), a specificity of 98% (95% CI: 90%–100%), a positive predictive value of 99% (95% CI: 94%–100%), and a negative predictive value of 75% (95% CI: 64%–85%); 7/164 (4%) examinations were inconclusive because of insufficient bone windows. The interobserver agreement was almost perfect (κ value, 0.92; 95% CI: 0.87–0.97).

CONCLUSION: eTCCD provides high diagnostic validity for the status of the major intracranial arteries. In particular, a normal vessel status reliably assessed by an experienced sonographer could supersede further imaging procedures. In patients with acute ischemic stroke not eligible for established angiographic techniques, eTCCD may be useful as an alternative imaging technique.

During the last decade, transcranial color-coded duplex sonography (TCCD) has been established as an alternative diagnostic technique for evaluation of the basal intracranial arteries. TCCD may help direct thrombolytic therapy in patients with acute ischemic stroke who are not eligible for standard imaging techniques such as MR angiography (MRA) or CT angiography (CTA).[1] A major limitation of TCCD is the absorption and dispersion of the sonographic signal intensity by the bony skull. Evaluation of the major arteries of the circle of Willis is not possible in up to 30% of patients because of insufficient transtemporal bone windows.[2-6]

In the present study, we sought to determine the diagnostic validity of echo-enhanced TCCD (eTCCD) as a routine technique in a large number of patients. Digital subtraction angiography (DSA) was used as the gold standard correlative imaging procedure.

Materials and Methods

We prospectively included all patients admitted to our neurology department for evaluation of cerebrovascular symptoms who underwent DSA. Patients with an acute stroke qualifying for thrombolytic therapy were not included in this study during their acute phases. Before the eTCCD examination, all included patients had a complete color-coded duplex examination of the extracranial carotid system and the vertebral arteries as well as a transcranial Doppler sonography (TCD) of the major arteries of the circle of Willis and of the vertebrobasilar arteries. This imaging is part of a routine stroke work-up for all patients admitted to the stroke unit of our institution. The 2 physicians (A.K., G.H.) who performed all eTCCD examinations for this study were not aware of the results of this routine stroke work-up and had only been informed if a patient was assigned to DSA. Before evaluation, all patients provided informed consent for participation in the study.

eTCCD

The eTCCD examinations were performed before DSA by 2 experienced physicians (A.K., G.H.). A complete eTCCD examination included evaluation of the anterior and vertebrobasilar circulations. The transtemporal approach was used to assess the anterior circulation.[7] The major arteries in the vertebrobasilar circulation were insonated by using the suboccipital access through the foramen magnum.[8] We used SH U 508A (Levovist, Schering, Berlin, Germany), an intravenous galactose and palmitic acid–based echo-enhancing contrast agent (EEA) for our study. Before EEA administration, an unenhanced TCCD was performed to identify the optimal acoustic bone windows. For the complete eTCCD examination, 2 doses of Levovist (300 mg/mL, 4 g per dose) were given intravenously via an antecubital access. The EEA was delivered continuously at an infusion rate of 900 mg/min by using an infusion pump (Medrad Pulsar Sonography Injection System, Medrad, Indianola, Pa).

The following arterial branches were assessed bilaterally via the transtemporal bone windows: C1 segments of the internal carotid arteries (ICAs); A1 and A2 segments of the anterior cerebral arteries (ACAs); M1 and M2 segments of the middle cerebral arteries (MCAs);

Received September 11, 2005; accepted after revision January 25, 2006.

From the Departments of Neurology (A.K., G.H., G.G.) and Neuroradiology (D.M., A.M., R.v.K.), University of Technology Dresden, Dresden, Germany; and the Department of Neurology (K.M.B.), Mayo Graduate School of Medicine, Mayo Clinic, Jacksonville, Fla.

A. Kunz and G. Hahn contributed equally to this study.

Please address correspondence to: Georg Gahn, MD, Department of Neurology, University of Technology Dresden, Fetscher Str 74, 01307 Dresden, Germany; e-mail: gahn@rcs.urz.tu-dresden.de

and P1 and P2 segments of the posterior cerebral arteries (PCAs), the anterior communicating arteries (AComAs), and the posterior communicating arteries (PComAs). Using the suboccipital approach, we evaluated the V4 segments of both the vertebral and the basilar arteries. The assessed arterial segments were found to be either normal or abnormal according to the Doppler-flow patterns. Criteria for abnormalities were increased mean flow velocity, retrograde flow, vessel-occlusion signals, or turbulent flow patterns.

The sonographic examinations were performed with an Acuson 128XP/4 (Siemens, Berlin and Munich, Germany) equipped with a 2.0/2.5-MHz transcranial sector scanner device. All eTCCD examinations were performed by using B-mode, pulsed-wave Doppler, and color velocity Doppler imaging mode. We used a standard insonation depth of 100 mm for the transtemporal approach and a depth of 120 mm for the suboccipital approach. The focus of the sample volume was adjusted to the appropriate depths of the individual arterial segments. During administration of Levovist, the pulse repetition frequency was increased to minimize aliasing and blooming artifacts. All eTCCD examinations were stored on super-VHS videotape for later off-line analysis.

DSA

All patients underwent DSA as the correlative imaging procedure. DSA was performed and interpreted by 3 experienced neuroradiologists (R.v.K., D.M., A.M.) blinded to the results of the eTCCD examinations. When possible, all patients underwent 4-vessel DSA. Criteria for abnormalities in DSA were stenoses of the extracranial arteries of at least 50% or any other pathologies that were found intracranially.

Data Analysis and Statistics

All eTCCD examinations were separately evaluated by 2 experienced reviewers (A.K., G.H.). At the time of evaluation, they were blinded to the patient's clinical diagnosis and the results of the extracranial duplex and TCD studies and the DSA. To correlate the findings of the eTCCD examinations with the DSA results, we used 2 different paradigms:

1) Diagnosis-Based Validation of eTCCD. On the basis of the analysis of the color-coded flow pattern and the Doppler spectra in all arterial segments that could be analyzed by eTCCD, each reviewer created a distinct eTCCD diagnosis of the intracranial arterial status for each eTCCD examination. According to the corresponding DSA results, the eTCCD diagnoses were classified as either true-negative, true-positive, false-negative, or false-positive. If the bone window was insufficient to allow a conclusive diagnosis, the examination was classified as not evaluable. On the basis of this categorization, we calculated the sensitivities, specificities, and positive and negative predictive values as the validating criteria for each reviewer's evaluation. Additionally, we determined the interobserver agreement between the 2 reviewers by using kappa statistics. Agreement was considered moderate if κ was between 0.41 and 0.6, substantial if κ was between 0.61 and 0.8, and almost perfect if κ was between 0.81 and 1.0.[9,10] Thereafter, the discordant eTCCD examinations were re-evaluated in a second consensus review, and the validating criteria were recalculated.

To further specify the validity of eTCCD in relation to the location of cerebrovascular abnormalities, we categorized all examinations according to the DSA diagnosis into the following 4 subgroups: normal findings, abnormalities in the extracranial anterior circulation, abnormalities in the intracranial circulation, and abnormalities in the vertebrobasilar circulation. Each examination was categorized to all eligible subgroups. For all subgroups, the validating criteria were recalculated.

2) Validation of eTCCD by Analyzing the Distinct Intracranial Arterial Segments. Another objective of this study was to assess the validity of eTCCD to detect abnormalities in distinct arterial segments of the intracranial circulation. Therefore, both reviewers separately assessed the status of all major arterial segments visualized by eTCCD. After comparing these results with the DSA findings, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value for all arterial segments. If an arterial segment was not examined either by eTCCD or by DSA, it was classified as "not done." In cases in which the arterial segment was visualized by DSA but not by eTCCD, it was classified as "not visible."

Results

During the 24-month study period, 132 consecutive patients were enrolled (40 women, 92 men; mean age, 58 $\pm$ 14 years; range, 19–86 years). For geographic reasons, all included patients were white; 121/132 patients (92%) underwent evaluation of the anterior circulation and 99/132 patients (75%) underwent evaluation of the vertebrobasilar circulation by eTCCD. Eighty-eight patients had evaluation of both anterior and posterior circulations by eTCCD. During the study period, no patient who underwent DSA at our institution was excluded from the study and no patient refused participation. No serious side effects (ie, anaphylactic reactions) were observed after administration of Levovist. The mean time interval between the eTCCD and DSA examination was 3 $\pm$ 3 days (median, 1.5 days). One hundred four of 132 patients underwent DSA and eTCCD evaluation once, and 26/132 patients were evaluated twice (24 following unilateral percutaneous transluminal stent protected angioplasty of ICA stenosis and 2 following embolization of an arteriovenous fistula). Another patient was evaluated 3 times because of bilateral ICA stent-protected angioplasty in 2 successive DSA procedures. This patient was examined before and after each intervention. Finally, 1 patient with a unilateral symptomatic high-grade MCA stenosis was evaluated 5 times. The lesion was not amenable to stent implantation and, therefore, was treated with angioplasty several times. Overall, we assessed 164 datasets consisting of an eTCCD and the correlative DSA-examination.

Subjective improvement in visualization of the intracranial arteries was noted during the administration of Levovist in most patients (data not shown).

For the assessment of neurologic deficits of the patients included, we used the National Institutes of Health Stroke Scale (NIHSS) score. The NIHSS score ranged between 0 and 19. Of all 132 patients, 119 had a NIHSS score of less than 8, which translates to a slight-to-moderate functional deficit. Eight patients were very moderately (NIHSS score, 8–11) compromised; 7 of them had pathologies in the extracranial parts of the carotids. Five patients had more severe neurologic deficits on admission (NIHSS score, $>$ 11). Among these patients, 3 had pathologies in the intracranial cerebral arteries (Table 1).

Table 2 shows the clinical spectrum of the patients included. Most patients (102/132) had cerebral ischemia or presented with reversible ischemic stroke symptoms. Eight patients presented with an asymptomatic critical ICA stenosis,

Table 1: Distribution of the clinical status (assessed by NIHSS on admission) of all patients enrolled and of the patients in different subgroups with pathologic finding

NIHSS on admission	All Patients (n = 132)	Pathologies on DSA			
		No (n = 24)	Extracranial (n = 72)	Intracranial (n = 27)	VA (n = 21)
<4	79	16	43	15	11
4–7	40	6	21	8	9
8–11	8	1	7	1	0
≥12	5	1	1	3	1

Note:—NIHSS indicates National Institutes of Health Stroke Scale score; DSA, digital subtraction angiography; VB, vertebrobasilar. Numbers of patients qualifying for the defined NIHSS ranges are shown.

Table 2: Clinical spectrum of the patients enrolled

	n
Embolic stroke	55
Transient ischemic attack	19
Low flow stroke	12
Asymptomatic ICA stenosis	8
Dissection	7
Intracerebral hemorrhage	7
Aneurysm	4
Vascular malformation	4
Stenosis/occlusion of basilar artery	4
Subarachnoid hemorrhage	3
Subclavian steal	3
Lacunar stroke	2
Other diagnoses	5

Note:—ICA indicates internal carotid artery.

Table 3: Diagnosis-based validation of all eTCCD-examinations (n = 164) in correlation to DSA

	Reviewer 1	Reviewer 2	Consensus
NE	4 (1–7)	4 (1–7)	4 (1–7)
Sensitivity	82 (75–90)	80 (72–88)	82 (75–90)
Specificity	96 (88–100)	98 (90–100)	98 (90–100)
PPV	98 (92–100)	99 (93–100)	99 (94–100)
NPV	75 (63–84)	73 (62–83)	75 (64–85)

Note:—PPV indicates positive predictive value; NPV, negative predictive value; NE, not evaluable; eTCCD, echo-enhanced transcranial color-coded duplex sonography. All values are shown in percent. Numbers in parentheses represent 95% confidence intervals.

Table 4: Agreement between reviewers 1 and 2 for all eTCCD-examinations (n = 164) using κ-statistics

Reviewer 1	Reviewer 2					
	NE	FN	FP	TN	TP	**Total**
NE	6	0	1	0	0	**7**
FN	0	17	0	0	1	**18**
FP	0	0	0	2	0	**2**
TN	1	0	0	53	0	**54**
TP	0	3	0	0	80	**83**
Total	**7**	**20**	**1**	**55**	**81**	**164**

Note:—NE indicates not evaluable; FN, false negative; FP, false positive; TN, true negative; TP, true positive; eTCCD, echo-enhanced transcranial color-coded duplex sonography. The κ-value is 0.92 (95%-confidence interval: 0.87–0.97).

for elective percutaneous transluminal stent-protected angioplasty. One patient with a subarachnoid hemorrhage due to an aneurysm at the bifurcation of the right M1 segment was assigned to both clinical entities. Five patients underwent DSA to rule out cerebrovascular origin of neurologic symptoms.

Of all 164 DSA examinations, 24 (15%) had no abnormalities, 98 (60%) had abnormalities of the extracranial carotid arteries, 32 (20%) had abnormalities in the intracranial circulation, and 21 (13%) had abnormalities in the vertebrobasilar circulation. Among the patients with abnormalities of the extracranial carotid arteries, most had unilateral (46 patients) or bilateral (18 patients) ICA stenoses or occlusions. Also represented in this subgroup were unilateral ICA dissections (4 patients), ICA aneurysms (2 patients), and common carotid artery occlusion (1 patient). Additionally, 1 patient with stenosis of the brachiocephalic trunk was included in this subgroup. In the subgroup with abnormalities of the intracranial circulation, most patients had stenoses or occlusions of intracranial arteries, with the MCA being the most commonly affected vessels (15 patients). Other locations of intracranial stenoses or occlusions were the intracranial ICA (6 patients), the ACA (2 patients), and the PCA (1 patient). One patient had a unilateral aneurysm located at the bifurcation of the right M1 segment, 1 patient had an aneurysm of the AComA, and 2 patients had an arteriovenous malformation. Another 2 patients presented with vasospasms following subarachnoid hemorrhage. The subgroup of abnormalities in the vertebrobasilar circulation consisted mostly of patients with stenoses or occlusions of the extra- or intracranial vertebral arteries (14 patients) as well as the basilar arteries (4 patients). Additionally, this subgroup included 3 patients with a vertebral artery dissection, 1 patient with posterior inferior cerebellar artery occlusion, 2 patients with a vertebrobasilar arteriovenous fistula, and 3 patients with a stenosis of the subclavian artery and steal phenomenon. A large number of patients included in our study had multiple pathologies of the brain-supplying arteries.

In summary, a larger part of patients (64/132) included in our study underwent DSA for the evaluation of stenoses or occlusions of the carotid arteries and subsequently underwent percutaneous transluminal stent-protected angioplasty.

Diagnosis-Based Validation of eTCCD. The sensitivities, specificities, positive predictive values, and negative predictive values are shown in Table 3. Both reviewers were unable to reach a conclusive diagnosis in 7/164 examinations (4%) because of insufficient bone windows. The mean age of those 7 patients (3 women, 4 men) was 71 ± 8 years, and they were significantly older ($P < .001$) than the other patients. Assessment of the interobserver agreement of all 164 eTCCD examinations revealed 8 discordant results. This refers to a κ value of 0.92 (Table 4). Because of the almost perfect agreement of the 2 reviewers' results, the subsequently presented results refer to the datasets obtained at the time of consensus review.

Table 5 summarizes the validation data obtained after subgroup analysis. In the subgroup of normal findings by DSA (n = 24), all patients were assessed as normal by eTCCD (specificity,100%; negative predictive value, 100%). The sensitivity,

Table 5: Diagnosis-based validation of eTCCD subgroups in correlation to DSA after consensus review

	Findings		Abnormalities		
	Normal (n = 24)	Abnormal (n = 140)	Extracranial (n = 98)	Intracranial (n = 32)	VB (n = 21)
N.E.	4 (0–21)	4 (1–8)	6 (2–13)	0 (0–11)	0 (0–16)
Sensitivity	N/A	82 (74–89)	83 (71–92)	81 (64–93)	76 (53–92)
Specificity	100 (85–100)	97 (84–100)	97 (84–100)	N/A	N/A
PPV	N/A	99 (94–100)	98 (89–100)	100 (87–100)	100 (79–100)
NPV	100 (85–100)	64 (49–77)	76 (61–88)	0 (0–46)	0 (0–52)

Note:—VB indicates vertebrobasilar; NE, not evaluable; PPV, positive predictive value; NPV, negative predictive value; N/A, not available; eTCCD, echo-enhanced transcranial color-coded duplex sonography; DSA, digital subtraction angiography. All values are shown in percent. Numbers in parentheses represent 95% confidence intervals.

Table 6: Visualization of the distinct arterial segments evaluable by eTCCD according to the separate assessment of the reviewers and after consensus review

Segment	Reviewer 1	Reviewer 2	Consensus
V4	99	99	99
M1	93	94	93
BA	94	88	91
P1	88	91	90
P2	87	91	89
C1	84	83	83
A1	84	81	82
M2	61	50	55
A2	48	42	45
AComA	27	24	26
PComA	23	25	24

Note:—V4 indicates V4-segment of the vertebral artery; M1/M2, M1-/M2-segment of the middle cerebral artery; BA, basilar artery; P1/P2, P1-/P2-segment of the posterior cerebral artery; C1–C1-segment of the internal carotid artery; A1/A2, A1-/A2-segment of the anterior cerebral arteries; AComA, anterior communicating artery; PComA, posterior communicating artery; eTCCD, echo-enhanced transcranial color-coded duplex sonography. All values are shown as percentages.

Table 7: Validation of eTCCD in comparison with DSA by analyzing the sensitivities, specificities, and positive and negative predictive values of the distinct arterial segments

Segment	Sensitivity	Specificity	PPV	NPV
M1	87 (81–94)	98 (96–99)	92 (87–97)	96 (94–98)
M2	76 (62–87)	100 (100–100)	100 (91–100)	95 (92–97)
C1	84 (75–91)	99 (99–100)	97 (90–100)	96 (94–98)
A1	77 (71–84)	97 (94–99)	94 (91–98)	85 (81–89)
A2	70 (35–93)	100 (100–100)	100 (59–100)	99 (97–100)
P1	74 (64–83)	99 (98–100)	96 (88–99)	92 (89–95)
P2	77 (64–88)	99 (98–100)	93 (81–99)	96 (94–98)
PComA	91 (81–97)	79 (68–88)	78 (66–87)	92 (82–97)
AComA	94 (86–98)	86 (42–100)	98 (92–100)	60 (26–88)
V4	78 (64–89)	99 (97–100)	92 (79–98)	96 (93–98)
BA	76 (50–93)	99 (97–100)	87 (60–98)	97 (94–100)

Note:—PPV indicates positive predictive value; NPV, negative predictive value; PComA, posterior communicating artery; AComA, anterior communicating artery; M1/M2, M1-/M2-segment of the middle cerebral artery; C1, C1-segment of the internal carotid artery; A1/A2, A1-/A2-segment of the anterior cerebral arteries; P1/P2, P1-/P2-segment of the posterior cerebral artery; V4, V4-segment of the vertebral artery; BA, basilar artery; eTCCD, echo-enhanced transcranial color-coded duplex sonography; DSA, digital subtraction angiography. The displayed values refer to the datasets obtained by both reviewers. All values are shown as percentages. Numbers in parentheses represent 95% confidence intervals.

specificity, positive predictive value, and negative predictive value in the subgroup of all extracranial pathologies as well as the sensitivity and positive predictive value in the subgroup of all intracranial pathologies are similar as to the results obtained for all examinations. The sensitivity in the subgroup of all vertebrobasilar pathologies is slightly lower compared with that of all examinations.

Validation of eTCCD by Segmental Intracranial Artery Analysis. The percentages of visualization of the distinct arterial segments by eTCCD are shown in Table 6. The V4 segments of the vertebral arteries, the M1 segments of the MCA, and the proximal part of the basilar artery could be visualized with the highest certainty. The basilar artery was visualized through the suboccipital transforaminal bone window to a mean depth of 97 ± 15 mm.

Table 7 summarizes the validation of those arterial segments usually visualized with eTCCD. The displayed values refer to the datasets obtained by both reviewers. Except for the PComA and AComA, excellent specificities (range, 97%–100%) and high sensitivities (range, 70%–87%) were calculated for all other segments with the best results for the M1 and C1 segments. The positive predictive values ranged between 92% and 100% except for the PComA (78%) and the basilar artery (87%). The negative predictive values also mostly exceeded the 90% values, with the exception of the A1 segments (85%) and the AComA (60%).

Discussion

The objective of this study was to assess the diagnostic validity of eTCCD in patients admitted to our department because of ischemic symptoms ascribed to cerebral arteries. Several groups have evaluated the diagnostic reliability of unenhanced as well as eTCCD in correlation with DSA, MRA, and CTA.[2,3,5,6,11-17] Among these different techniques, DSA remains the gold standard and allows the most precise reproduction of the cerebral circulation in comparison with the real anatomy of the cerebral blood vessels. To our knowledge, this is the largest prospective study validating eTCCD findings with DSA.

The improvement of the diagnostic potential of TCCD by the use of EEA has been widely accepted.[3,5,6,11,16,17] In our study, we performed eTCCD examination exclusively. The rationale for this approach was the potential time delay, which might occur through an initial unenhanced TCCD examination. In patients with acute stroke symptoms, a fast, reliable, and accurate finding is fundamental for the optimal treatment. Additionally, patients with stroke at their typical ages have limited acoustic bone windows. Considering the gain of time through the use of EEA at the beginning and the relatively low risk of EEA, we consider this approach reasonable and justified.

The preponderance of men in the present study (male/female ratio, 2.3) reflects the fact that more men than women underwent DSA at our institution during the study period. This is consistent with the higher stroke incidence in white men than in white women at that age (58 ± 14 years), which we have obtained as the mean age of our study population.[18] In

addition, the imbalance toward men is attributable to the fact that a larger part of our study population underwent DSA for evaluation of critical ICA stenosis. The prevalence of carotid stenosis is higher in men than in women.[19] The relatively young mean age of our patients is explained by the fact that the DSA was exclusively performed with the intention of a subsequent intervention.

Most enrolled patients were admitted with acute ischemic stroke symptoms and had slight-to-moderate neurologic deficits (90% of patients with NIHSS score < 8). This finding is of practical importance because this population of patients with acute ischemic stroke has the highest probability of having a favorable outcome.[20,21] This population of patients is the primary target for acute stroke therapy.

By eTCCD, we found a conclusive diagnosis in 96% (157/164) of all eTCCD examinations. The remaining 7 patients had insufficient bone windows. It has been reported that the rate of successful recording of blood flow signals by transcranial sonography decreases with advancing age.[22] The percentage of conclusive diagnoses in our study is obviously higher than that previously reported.[6,11,16,17] In contrast to those studies, we administered Levovist to all patients regardless of their bone windows. However, it has to be considered that the sex ratio of our study population was imbalanced, with a strong preponderance of men. Women have a higher prevalence of insufficient acoustic bone windows than men.[23] Also, the relatively young mean age of the patients included in our study could have contributed to the low number of insufficient bone windows.[24]

Overall, validation of eTCCD diagnosis in comparison with DSA revealed an excellent specificity as well as positive predictive value with only 1 false-positive diagnosis of 164 examinations. Furthermore, when considering only patients with normal findings by DSA, we were able to identify all of these patients by eTCCD. We conclude that 1 domain of eTCCD could be a highly specific identification of a normal intracranial arterial status. Therefore, if an experienced sonographer detects no abnormalities by using eTCCD in a patient with sufficient bone windows, it is reasonable not to pursue further imaging procedures.

With regard to the reliability of eTCCD to detect abnormalities in the intracranial arterial vasculature, we obtained an overall high sensitivity of 82%. Herein, most false-negative eTCCD examinations represented a modified intracranial blood flow pattern because of critical extracranial ICA stenoses or occlusions. In this context, one should also consider that DSA may not necessarily reflect the true intracranial collateral flow pattern under resting conditions. One characteristic intracranial collateral flow pattern in patients with critical unilateral ICA stenosis is prolonged cardiac cycle–independent cross-filling of the A1 segment ipsilateral to the stenosis. It is conceivable, for example, that during the DSA procedure, injection of contrast medium at a high flow rate into the contralateral distal ICA could induce a temporary cross flow through the ipsilateral A1 segment. This phenomenon could occur in patients with already compromised but not yet reversed blood flow through the A1 segment ipsilateral to the stenosis. This would not have been recognized under resting conditions by eTCCD. Also, in our study, none of the reviewers had been aware of the extracranial duplex status of any included patient. The sonographer's knowledge of an extracranial stenosis or occlusion could certainly increase the sensitivity to detect alterations in the intracranial blood flow.

Another group of false-negative results was from abnormalities in smaller branches of the intracerebral vasculature (ie, branches distal to the M2 segments, the posterior inferior cerebellar artery, or the AComA). These segments were too small to be assessed by eTCCD. This hypothesis is strengthened by the percentages of visualization for the distinct arterial segments displayed in Table 6. The M2 segments, for example, can be evaluated in only 55% of all eTCCD examinations. For branches distal to the M2 segments, this percentage probability might be lower.

Therefore, we conclude that validation of eTCCD compared with DSA reveals an overall high sensitivity. Pitfalls for the accurate evaluation of the intracranial vasculature by eTCCD could be an altered blood flow pattern due to critical extracranial ICA stenoses or abnormalities in smaller arterial branches.

Table 6 demonstrates the dependence of visualization of the distinct intracranial arterial segments by eTCCD on their diameters. The proximal segments of the MCA, ACA, and PCA are visible with a higher certainty than their distal branches (M2, A2, and P2 segments, respectively). Additionally, for the MCA as well as the ACA, the overall sensitivities of the distal branches are slightly lower than those of the proximal segments. Together with the higher visibilities, this suggests a higher diagnostic validity of the main stems of the major cerebral arteries, in particular the MCA. These results have an important implication on the efficiency of eTCCD in clinical practice. The MCA is the most commonly affected artery in ischemic stroke syndromes. Especially, embolic strokes occur mostly in the MCA territory. Massive hemispheric infarction due to acute occlusion of the proximal MCA and poor collateral flow carries a high mortality. The only potential therapy for these patients is early administration of thrombolysis. Although the knowledge of the patency of the MCA is not required for the initiation of thrombolytic therapy in acute ischemic stroke, the ability to identify clot in the proximal MCA may help in deciding to pursue thrombolytic therapy in individual patients. Moreover, an experienced sonographer is able to diagnose an MCA occlusion by eTCCD within 5 minutes. Because of the necessity of performing a native computed tomography of the brain and evaluating the functional deficit in a patient with acute stroke before initiation of thrombolytic therapy, an additional eTCCD examination does not necessarily delay the initiation of thrombolytic therapy. Therefore, we propose that eTCCD is an efficient primary as well as follow-up imaging procedure for patients with acute ischemic stroke syndromes referable to the MCA territory. Thus, eTCCD is a valuable alternative bedside technique applicable to patients who are not eligible for standard imaging techniques (eg, DSA, CTA, or MRA) because of either impaired renal function or poor cooperation.

In the subgroup of patients with vertebrobasilar pathologies, the sensitivity for eTCCD was slightly lower. The lower sensitivity may be partly due to technical limitations in following the course of tortuous arteries through the suboccipital window. Only a small percentage of patients included in our study had vertebrobasilar abnormalities. Also, the sonogra-

phers performing this study used the eTCCD examinations exclusively for evaluating the vertebrobasilar vessel status. Additional knowledge of the hemodynamics in the extracranial vertebral arteries assessed by extracranial duplex sonography might improve the results. However, the objective of this study was to assess the validity of eTCCD based exclusively on transcranial and suboccipital duplex findings. Therefore, the presented results of vertebrobasilar pathologies are preliminary. The mean transforaminal insonation depth of 97 ± 15 mm enables eTCCD evaluation of only the proximal two thirds of the basilar artery.[25,26] This is a major limitation in patients with a suspected basilar artery occlusion. On the basis of the small population of patients with suboccipital abnormalities examined in this study, we conclude that in patients with a clinical syndrome suggestive of a vertebrobasilar disease, eTCCD alone might not be sufficient and additional imaging procedures should be considered.

One potential shortcoming of our study is the fact that owing to the geographic location of our neurology department, only whites were included. The existence of racial differences in the temporal bone window thicknesses and its interference with the transtemporal insonation conditions are known.[27] This obviously limits the generalizability of our study. Application of our study paradigm to a racially mixed study population would be valuable.

Conclusion

In summary, our results provide convincing evidence to support use of eTCCD as a highly efficient imaging technique to evaluate the status of the major intracranial cerebral arteries. We have demonstrated an excellent specificity in the identification of a normal intracranial arterial status. Our data suggest that if an experienced sonographer detects no abnormalities by using eTCCD in a patient with sufficient bone windows, it is reasonable to forego further imaging procedures. In addition, we observed a high reliability in the diagnosis of proximal MCA pathologies. Furthermore, this procedure is minimally invasive and easily applicable at the bedside; these features make eTCCD a useful diagnostic tool.

Acknowledgments

We thank Rainer Koch, PhD (Institute for Medical Biometrics, University of Technology Dresden) for statistical advice.

References

1. Gahn G, von Kummer R. **Ultrasound in acute stroke: a review.** *Neuroradiology* 2001;43:702–11
2. Baumgartner RW, Baumgartner I, Mattle HP, et al. **Transcranial color-coded duplex sonography in the evaluation of collateral flow through the circle of Willis**. *AJNR Am J Neuroradiol* 1997;18:127–33
3. Gerriets T, Seidel G, Fiss I, et al. **Contrast-enhanced transcranial color-coded duplex sonography: efficiency and validity.** *Neurology* 1999;52:1133–37
4. Seidel G, Kaps M, Gerriets T. **Potential and limitations of transcranial color-coded sonography in stroke patients**. *Stroke* 1995;26:2061–66
5. Zunker P, Wilms H, Brossmann J, et al. **Echo contrast-enhanced transcranial ultrasound: frequency of use, diagnostic benefit, and validity of results compared with MRA.** *Stroke* 2002;33:2600–33
6. Gahn G, Gerber J, Hallmeyer S, et al. **Contrast-enhanced transcranial color-coded duplexsonography in stroke patients with limited bone windows.** *AJNR Am J Neuroradiol* 2000;21:509–14
7. Bogdahn U, Becker G, Winkler J, et al. **Transcranial color-coded real-time sonography in adults.** *Stroke* 1990;21:1680–88
8. Becker G, Lindner A, Bogdahn U. **Imaging of the vertebrobasilar system by transcranial color-coded real-time sonography**. *J Ultrasound Med* 1993;12:395–401
9. Landis JR, Koch GG. **The measurement of observer agreement for categorical data.** *Biometrics* 1977;33:159–74
10. Landis JR, Koch GG. **An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers**. *Biometrics* 1977;33:363–74
11. Baumgartner RW, Arnold M, Gonner F, et al. **Contrast-enhanced transcranial color-coded duplex sonography in ischemic cerebrovascular disease**. *Stroke* 1997;28:2473–78
12. Baumgartner RW, Mattle HP, Schroth G. **Assessment of >/=50% and <50% intracranial stenoses by transcranial color-coded duplex sonography.** *Stroke* 1999;30:87–92
13. Gahn G, Hahn G, Hallmeyer-Elgner S, et al. **Echo-enhanced transcranial color-coded duplexsonography to study collateral blood flow in patients with symptomatic obstructions of the internal carotid artery and limited acoustic bone windows.** *Cerebrovasc Dis* 2001;11:107–12
14. Gerriets T, Goertler M, Stolz E, et al. **Feasibility and validity of transcranial duplex sonography in patients with acute stroke**. *J Neurol Neurosurg Psychiatry* 2002;73:17–20
15. Kenton AR, Martin PJ, Abbott RJ, et al. **Comparison of transcranial color-coded sonography and magnetic resonance angiography in acute stroke**. *Stroke* 1997;28:1601–06
16. Nabavi DG, Droste DW, Kemeny V, et al. **Potential and limitations of echo-contrast-enhanced ultrasonography in acute stroke patients: a pilot study**. *Stroke* 1998;29:949–54
17. Postert T, Braun DW, Meves S, et al. **Contrast-enhanced transcranial color-coded sonography in acute hemispheric brain infarction.** *Stroke* 1999;30:1819–26
18. Howard G, Howard HV. **Distribution of stroke: heterogeneity of stroke by age, race, and sex.** In: Mohr P, Choi DW, Grotta JC, eds. *Stroke: Pathophysiology, Diagnosis, and Management*. Philadelphia: Churchill Livingstone; 2004:3–12
19. Mathiesen EB, Joakimsen O, Bonaa KH. **Prevalence of and risk factors associated with carotid artery stenosis: the Tromso Study.** *Cerebrovasc Dis* 2001;12:44–51
20. Adams HP Jr, Davis PH, Leira EC, et al. **Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST).** *Neurology* 1999;53:126–31
21. Adams HP Jr, Leclerc KC, Bluhmki E, et al. **Measuring outcomes as a function of baseline severity of ischemic stroke.** *Cerebrovasc Dis* 2004;18:124–29
22. Itoh T, Matsumoto M, Handa N, et al. **Rate of successful recording of blood flow signals in the middle cerebral artery using transcranial Doppler sonography**. *Stroke* 1993;24:1192–95
23. Marinoni M, Ginanneschi A, Forleo P, et al. **Technical limits in transcranial Doppler recording: inadequate acoustic windows.** *Ultrasound Med Biol* 1997;23:1275–77
24. Hashimoto H, Etani H, Naka M, et al. **Assessment of the rate of successful transcranial Doppler recording through the temporal windows in Japanese with special reference to aging and sex.** *Nippon Ronen Igakkai Zasshi* 199;29:119–22
25. Schulte-Altedorneburg G, Droste BW, Popa V, et al. **Visualization of the basilar artery by transcranial color-coded duplex sonography: comparison with postmortem results**. *Stroke* 2000;31:1123–27
26. Brunner-Beeg F, von Reutern GM. **Color duplex ultrasonography of the intracranial vertebro-basilar system: improved imaging by echo signal enhancement** [in German]. *Ultraschall Med* 1999;20:83–86
27. Halsey JH. **Effect of emitted power on waveform intensity in transcranial Doppler.** *Stroke* 1990;21:1573–78