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

Georg Gahn^a Gabriele Hahn^a Susanne Hallmeyer-Elgner^a
Alexander Kunz^a Torsten Straube^b Holger Bourquain^b Heinz Reichmann^a
Rüdiger von Kummer^b

Departments of ^aNeurology, and ^bNeuroradiology, University of Technology Dresden, Germany

Key Words

Doppler duplex ultrasonography · Transcranial color-coded duplexsonography · Carotid stenosis · Contrast media · Collateral circulation · Ischemic stroke

Abstract

We prospectively evaluated 30 consecutive patients with echo-enhanced transcranial color-coded duplexsonography (TCCD) and correlative transfemoral digital subtraction angiography to assess the diagnostic efficacy of echo-enhanced TCCD for evaluation of collateral pathways through the circle of Willis in patients with limited acoustic bone windows and critical symptomatic carotid disease. Echo-enhanced TCCD detected collateral blood flow through the anterior communicating artery in 16 of 18 patients (sensitivity 89%, 95% CI 65–99%) and was false positive in one out of 12 patients without collateral flow (specificity 92%, 95% CI 59–100%). For the posterior communicating artery, sensitivity was 11/14 (79%, 95% CI 49–95%) and specificity was 15/16 (94%, 95% CI 70–100%). Echo-enhanced TCCD enables to study collateral blood flow through the communicating arteries of the

circle of Willis with high sensitivity and specificity in patients with obstructions of the internal carotid artery and limited acoustic bone windows.

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Introduction

In patients with severe internal carotid artery (ICA) stenosis or occlusion, the most important source of collateral flow to the affected hemisphere are the contralateral ICA and the vertebrobasilar arteries via the communicating arteries of the circle of Willis [1]. Collateral flow through the anterior communicating artery (Acom) with retrograde flow in the A1 segment on the side of carotid disease depends on an intact anterior half of the circle of Willis. Many minor variations in the circle of Willis hinder this collateral pathways. The vertebrobasilar system may supply the middle and the anterior cerebral artery (MCA and ACA) territory through the ipsilateral posterior communicating artery (Pcom). The Pcom is less often developed than the Acom [2]. Competent collateral flow has been shown to reduce the risk of subsequent cerebral

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Georg Gahn, MD
Department of Neurology, University of Technology Dresden
Fetscher Strasse 74, D–01307 Dresden (Germany)
Tel. + 49 351 458 3565, Fax + 49 351 458 4365
E-Mail gahn@rcs.urz.tu-dresden.de

ischemia as well as the risk of ischemia during carotid endarterectomy and should be analyzed before intervention [3].

In patients with critical carotid stenosis or occlusion, conventional transcranial Doppler (TCD) is highly sensitive to demonstrate collateral pathways through the circle of Willis [4, 5]. Digital subtraction angiography (DSA), however, remains the gold standard for visualization of the intracranial vasculature. Transcranial color-coded duplexonography (TCCD) is a diagnostic tool that potentially improves ultrasound evaluation of the intracranial arteries by permitting direct visualization of the vessels, a feature which is not possible with conventional TCD [6]. Unenhanced TCCD has been shown to be an effective method for demonstrating collateral pathways in patients with carotid stenosis [7, 8]. However, thickening of the temporal bone in stroke age patients, more in women compared to men and in non-Caucasians, may obviate detection of the circle of Willis in 20–30% of subjects [9, 10]. Both TCD and TCCD require a good temporal acoustic window to insonate the middle cerebral artery (MCA) and the circle of Willis.

Ultrasound echo-enhancing agents have been successfully used to overcome this limitation [11–14]. In this study, we evaluated the effectiveness of a galactose/palmitic-acid-based echo-enhancing agent (Levovist®; Schering, Berlin, Germany) for visualizing collateral pathways through the circle of Willis by TCCD in patients with hemispheric ischemic symptoms, critical carotid disease and inadequate acoustic bone windows. Our investigation was designed to provide the sensitivity and specificity of echo-enhanced TCCD using DSA as gold standard.

Materials and Methods

We selected all patients during routine stroke work-up in our institution. All patients had a complete ultrasound evaluation of the carotid system and a TCCD study. Our routine ultrasound studies for the carotid system include performance of one indirect noninvasive test (periorbital directional Doppler ultrasonography) and of three direct tests: colorflow imaging, duplex imaging (B-mode/pulsed-wave Doppler examinations) and continuous-wave Doppler ultrasonography.

Patients eligible for inclusion into the study had to fulfill two main criteria. (1) Critical symptomatic carotid stenosis with $\geq 90\%$ lumen diameter reduction (corresponding to a residual lumen diameter ≤ 1.0 mm) or carotid occlusion. In this patient group, the obstructed ICA does not supply any significant flow volume to the affected hemisphere. Therefore, these patients completely depend on collateral flow to the affected hemisphere and may serve as a model for evaluation of collateral flow through the circle of Willis [15]. (2) No detectable colorflow signals of the circle of Willis by un-

enhanced TCCD due to limited acoustic windows. One of three independent experienced investigators (G.G., S.H.-E., G.H.) made the diagnosis of limited bone windows.

During the period from January 1997 to December 1999, we enrolled 30 consecutive patients (7 women, 23 men, mean age 63.8 ± 12.1) into the study. Twenty-eight patients had unilateral disease (16 stenoses, 12 occlusions), 2 patients had bilateral disease (1 bilateral occlusion, 1 occlusion on one side and critical stenosis on the other). We evaluated 17 patients during normal work-up for a recent ischemic event. In these patients, the mean time interval between onset of cerebral ischemia and echo-enhanced TCCD/DSA was 2.84 ± 3.27 days, 9/17 patients were evaluated within 24 h. The remaining patients had a remote ischemic event on the side of the carotid disease within the last 6 months.

TCCD Examination

Echo-enhanced TCCD was performed by three experienced physicians (G.G., S.H.-E., G.H.), details of the examination procedure are described elsewhere [16]. Four patients received two bolus injections of the echo-enhancing agent (2×2.5 g Levovist, concentration 300 mg/ml), the remaining a single continuous infusion of 4 g Levovist (concentration 300 mg/ml) over 5 min, which was found to provide better colorflow data because of a less prominent 'blooming effect'. The blooming effect causes echoes from moving blood to spill over vessel wall margins and creates overblown caricatures of the vascular pathways [17]. Continuous infusion of the microbubble echo-enhancing agent provides prolonged and uniform enhancement of Doppler signals and improves image quality by minimizing saturation artifacts [18]. Both sides of the circle of Willis were evaluated separately through each temporal window. In a first step, the examiner tried to identify all branches of the circle of Willis including the M1, A1 and A2, as well as the P1 and the P2 segments of the MCA, ACA and the posterior cerebral artery (PCA), respectively. For the evaluation of collateral flow, we analyzed colorflow signals according to flow direction and turbulence in the A1 segments of the ACA. We also analyzed the P1 segments of the PCA and the Pcom for turbulent flow. We further evaluated these vascular segments with duplex spectral waveform analysis. The TCCD diagnosis of collateral flow through the Acom was based on the detection of retrograde flow in the A1 segment on the side of the carotid disease. The diagnosis of collateral flow through the Pcom was based either (1) on the combined findings of visual detection of the artery itself and turbulent flow in this segment or (2) on the visual detection of the artery itself without turbulent flow in this segment, but with turbulent flow in the P1 segment of the side of carotid obstruction.

The examiner was blinded to the results of DSA. All echo-enhanced TCCD studies were recorded on super VHS videotape. Ultrasound examinations were performed with an AUCSON 128XP/4 with a 2.0/2.5-MHz transcranial sector scanner device. All TCCD data were analyzed off-line by two independent investigators (G.G., G.H.) blinded to the results of the DSA results. The analyses were then compared, and, if disagreements were found, the data were reviewed collaboratively to reach a final consensus.

DSA

All patients underwent DSA as correlative imaging studies. DSA were performed and read by 3 neuroradiologists (T.S., H.B., R.v.K.) blinded to the results of the echo-enhanced TCCD. All patients underwent four-vessel angiography for evaluation of all collateral pathways. Anatomic information recorded on a standardized data

collection sheet included the site of carotid obstruction and the measurement of stenosis in ipsilateral and contralateral carotid arteries.

Measurements of stenoses were expressed as percent stenosis of the narrowest luminal diameter relative to the diameter of the distal ICA. Whether there was collateral flow present through the Acom or through Pcom was documented in a dichotomous way both for TCCD and DSA studies. As for the TCCD analyses, different findings were reviewed collaboratively to reach a final consensus. The mean time interval between DSA and TCCD was 2.7 ± 2.5 days.

Results

In all patients, echo-enhanced TCCD enabled full visualization of the circle of Willis bilaterally. The mean duration of echo-enhancement after continuous infusion was 6 min 55 s with a range of 3 min 5 s to 10 min 40 s. In the patients with bolus injections, the duration was 2 min 45 s to 5 min 55 s.

In 18/30 patients, DSA showed collateral flow through the Acom (fig. 1c), which was visualized by echo-enhanced TCCD in 16 patients (89% sensitivity; fig. 1a, b). Echo-enhanced TCCD was correct in 11/12 patients, in whom DSA showed no collateral flow through the Acom (92% specificity).

Echo-enhanced TCCD identified 11/14 patients with angiographically proven collateral flow through the Pcom (79.0% sensitivity; fig. 1a, b, d). In 16 patients, DSA did not show collateral flow through the Pcom, which was suggested by echo-enhanced TCCD in 15 patients (94% specificity; table 1).

In 1 patient with unilateral carotid occlusion, TCCD showed increased flow velocities in the Pcom, which was taken as evidence for collateral flow through the Pcom. DSA, however, documented a hypoplastic Pcom which did not contribute significant flow to the MCA territory.

Disagreements between DSA and echo-enhanced TCCD concerning the determination of collateral flow through the Acom by TCCD occurred in 2 patients. In one of these with a unilateral ICA occlusion, slight vertical tilting of the ultrasound probe led to different flow directions in a region where one would typically expect to find the A1 segment. Depending on the probe position, the A1 on the side of stenosis appeared to be retro- or antegrade (fig. 2a–d). There were no increased blood flow velocities detectable in the contralateral A1. However, by insonation from the contralateral side, there was obvious retrograde flow through the A1 segment on the side of the carotid occlusion. By DSA, the A1 was obviously retrograde, but formed a loop at its origin from the ICA. In this selected patient, the close spatial relationship between the

Table 1. Echo-enhanced TCCD findings compared to DSA

	Acom	%	95% CI	Pcom	%	95% CI
Sensitivity	16/18	89	65–99	11/14	79	49–95
Specificity	11/12	92	59–100	15/16	94	70–100
Accuracy	27/30	90	73–98	26/30	87	69–96
Acom/Pcom: collateral flow through the Acom/Pcom.						

two arms of the A1 segment may have caused the confusing TCCD findings. Additionally the blooming effect may worsen differentiation between vessels by disrupting vessel borders.

In the 2 patients with bilateral carotid artery occlusion, TCCD detected collateral flow through the Pcom bilaterally, confirmed by DSA. However, in one of these patients, DSA suggested also additional retrograde flow in one A1 segment. There were no early films available for verification. The echo-enhanced TCCD showed bilateral antegrade A1 segments, and both ultrasound readers felt highly confident with their findings.

No serious adverse events occurred after application of Levovist.

Discussion

Transcranial ultrasound, both TCD and TCCD, are powerful tools for the assessment of collateral flow through the circle of Willis. In patients with acute hemispheric ischemic events, ultrasound studies of intracranial hemodynamics can provide important information. Similarly, in patients with subacute or chronic events, transcranial ultrasound could be used to define the type of ischemic injury.

Acoustical bone windows of stroke patients may be limited or nonexistent, restricting the applicability of routine transcranial ultrasound. Our patients had either severe ICA stenosis or occlusion. Echo-enhanced TCCD showed the circle of Willis on the side of concern in all subjects who had no identifiable intracranial vessels in the unenhanced study.

We found echo-enhanced TCCD to be highly effective for evaluation of collateral blood flow in critical carotid obstruction. Disagreements between echo-enhanced TCCD and DSA may be explained by the blooming effect [17]. The blooming effects of the echo-enhancing agent

causes anatomical disruption of the vessel borders. This phenomenon impairs the anatomical resolution of the colorflow data and may lead to uncertainties in vessel identification. Figure 2 illustrates this assumption in a patient with a tortuous vessel segment, in whom slight vertical tilting of the ultrasound probe led to different colorflow findings. In another patient with bilateral carotid artery occlusion, we did not find an explanation for the differences between echo-enhanced TCCD and DSA findings. In this patient, DSA did not provide sufficient data to confirm retrograde flow through the left A1 segment. We interpreted complete filling of both A1 segments without filling of the A2 segments and slightly delayed filling of the left MCA on the earliest available film as evidence for a retrograde left A1 segment. Echo-enhanced TCCD undoubtedly showed bilateral antegrade A1 segments. However, we performed the ultrasound study 5 days after the DSA. In the interim, sufficient collateral flow through the left Pcom may have developed to also provide antegrade flow through the left A1 segment. Another reason might be a misinterpretation of the DSA. DSA only provides one set of real-time data during the procedure, afterwards

data analysis is based on single films. Since echo-enhanced TCCD provides continuous real-time data stored on video tape, it may better allow assessment of dynamic flow processes.

In a typical stroke population, Levovist can increase the sensitivity of TCCD to detect the circle of Willis from 71.3 to 91.6% [19]. In our patient group, we had no patient in whom Levovist failed to detect the circle of Willis. We evaluated predominantly male patients. The prevalence of > 80% carotid stenosis is twice as high in males than in females, which explains the sex distribution in our study [20]. Since the acoustic bone windows are generally better in males than in females, the sex relationship of our patients may have contributed to the good effect of Levovist. Otherwise we would have expected Levovist to fail in some patients with respect to visualization of the entire circle of Willis. Another reason for its good effect could be the relative young age of 63.8 ± 12.1 years in our patient group. As a university hospital, we may not see a typical stroke-aged population, but relatively younger patients.

In their study with unenhanced TCCD Baumgartner et al. found a sensitivity of 98% and a specificity of 100% for detection of collateral flow through the Acom, and 84% sensitivity and 94% specificity for the Pcom [8]. These values are higher than ours, which might be related to the blooming effect of the echo-enhancing agent.

Martin et al. [7] did not correlate their unenhanced TCCD findings with DSA; they found collateral flow patterns in only 60% of patients with critical carotid stenosis or occlusion. By echo-enhanced TCCD and by DSA, we had 8 patients without detectable collateral flow through the Acom or Pcom, which correlates with anatomical studies [2].

A draw back of the echo-enhancing agent is the short half-time in the circulation when given as a bolus injection. When using the continuous infusion technique rather than the bolus injection, the recorded duration of echo-enhancement was sufficiently long to evaluate the entire circle of Willis from both sides of the skull.

Alternative noninvasive techniques for evaluation of the circle of Willis are spiral CT angiography and MR angiography. Direction of flow cannot be displayed by spiral CT angiography, which limits its applicability to evaluation of collaterals. MR angiography, however, is able to demonstrate the direction of flow with phase contrast sequences [21].

Because echo-enhanced TCCD can be done safely by the bedside even in uncooperative patients, it appears a sound and reliable examination for patients with severe carotid disease in the acute stroke phase. Prior to endar-

Fig. 1. a Echo-enhanced TCCD in a patient with unilateral ICA stenosis suggesting collateral flow through the Acom and the Pcom (for orientation see **b**). The arrow points to the A1 segment on the side of ICA obstruction. The red colorflow signal in this segment indicates retrograde flow directed to the side of ICA obstruction. Normally, flow in this segment would be directed towards the midline encoded by a blue colorflow signal. Note the turbulent flow in 3 arterial segments (short arrows): (1) in the A1 segment contralateral to the side of carotid obstruction; (2) on the side of carotid obstruction in the P1 segment, and (3) in the Pcom, suggesting collateral flow through these vessels. **c/d** Corresponding DSA (anteroposterior and lateral view) confirming collateral flow through the Acom and Pcom.

Fig. 2. Disagreement between echo-enhanced TCCD and DSA. **a** Echo-enhanced TCCD shows red-coded colorflow signal in the A1 segment on the side of carotid stenosis suggesting retrograde flow in this segment (arrow). **b** Slight vertical tilting of the ultrasound transducer shows blue-coded colorflow signal suggesting an antegrade flow in the A1 segment (arrow) on the side of stenosis. **c** Insonation from the contralateral side identifies only retrograde flow signals suggesting collateral flow from the normal side to the side of carotid obstruction (arrow). Note the 'blooming effect' which causes echoes from moving blood to spill over vessel wall margins and creates overblown caricatures of the vascular pathways. This artifact impairs visual identification of the arterial segments. **d** DSA demonstrates retrograde flow on the side of stenosis (arrow). There is marked tortuosity of the A1 segment which may, in combination with the blooming effect, explain the confusing colorflow signals in this vessel segment.

terectomy, echo-enhanced TCCD may help to avoid using angiography. Echo-enhanced TCCD is a promising technology, but needs further refinement before it is of clinical value.

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