Echocontrast-Enhanced Ultrasound of Extracranial Internal Carotid Artery High-Grade Stenosis and Occlusion

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Background and Purpose—Proper assessment of extracranial internal carotid artery high-grade stenosis and occlusion by extracranial color-coded duplex sonography (ECCD) is occasionally made difficult by shadowing, an unfavorable insonation angle, low flow velocity or volume, or a deep insonation depth. In these cases, echocontrast could be helpful to quantify the degree of stenosis and to diagnose occlusion.

Methods—We investigated 17 arteries with poor precontrast investigation conditions and suspected high-grade stenosis or occlusion by contrast-enhanced ECCD.

Results—Compared with the precontrast scans, echocontrast allowed for significantly more segments to be evaluated by pulsed Doppler sonography ($P<0.001$) and for longer lumen segments to be displayed on color mode ($P<0.001$). Because it was now possible to place the sample volume right into the jet of the stenosis, the maximal flow velocity registered increased in all patients with stenosis.

Conclusions—Echocontrast-enhanced ECCD of the carotid arteries is helpful for stenosis classification in a small group of preselected patients with poor original examination conditions. **(*Stroke*. 1999;30:2302-2306.)**

Key Words: carotid arteries ■ contrast media ■ occlusion ■ stenosis ■ ultrasonography

Extracranial color-coded duplex sonography (ECCD) is a noninvasive, highly accurate procedure to detect stenoses and occlusions of the carotid arteries.[1–3] The refined spatial resolution and the appearance of color-coded flow signals help to adequately place the Doppler sample volume in the different vessel segments of interest. Peak systolic flow velocity is an important and highly reproducible parameter for stenosis quantification.[4,5] Patients with symptomatic extracranial high-grade carotid artery stenosis generally undergo surgery. In occlusions, surgery is only possible in exceptional cases. ECCD serves as a screening procedure, eventually followed by intra-arterial angiography, when carotid artery endarterectomy is scheduled. In many specialized centers, carotid endarterectomy is already performed on the basis of ECCD findings without angiography.[6–10] In conjunction with continuous-wave Doppler of the periorbital arteries and transcranial Doppler sonography, ECCD plays a key role in the accurate quantification of the degree of stenosis, assessment of the exact location of the stenosis in relation to the flow divider, and discrimination of subtotal stenosis from occlusion.[11,12]

ECCD is occasionally made difficult by ultrasonic shadowing of calcified plaques, the thickness of the tissue between the probe and the artery, an unfavorable insonation angle, and the low flow volume or low flow velocity in very tight stenosis. Echocontrast agents that are able to survive pulmonary and capillary transit and to improve the echogenicity of the flowing blood were developed to overcome these limitations. Levovist (Schering AG) currently is the most widely used echocontrast agent in neurosonology. After preparation, Levovist is a suspension of air-filled microbubbles adherent to galactose granules with a palmitic acid coating and a median diameter of 3 μm. Presently, attempts are made to extend the diagnostic window of this echocontrast agent by continuously infusing it intravenously.

In neurology, echocontrast agents are mainly used for transcranial color-coded ultrasound enhancement. There are only a few reports on the use of echocontrast agents in the extracranial cerebral vasculature.[13–16] In the present study, we describe the benefits and pitfalls of echocontrast enhancement in patients with extracranial carotid artery high-grade stenosis or suspected subtotal stenosis or occlusion.

Subjects and Methods

We prospectively investigated 17 carotid arteries of 15 patients. In the patients selected for extracranial echo enhancement, either peak systolic flow velocity measured in the extracranial internal carotid artery (ICA) did not correspond to the severity of narrowing expected from indirect signs upstream or downstream, or the location (intracranial or extracranial) of a suspected ICA stenosis was not clear, or a definite discrimination between occlusion and subtotal

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stenosis could not be made. In the study time period of 4 months, a total of 637 patients were investigated in our neurosonological laboratory. Of these, 133 patients had extracranial carotid artery occlusion or high-grade stenosis. All patients received a continuous-wave Doppler investigation of their neck arteries and of the supratrochlear arteries, including compression tests of the facial and the superficial temporal arteries. Furthermore, they underwent transcranial Doppler sonography or transcranial color-coded duplex sonography of the large basal arteries. The carotid arteries and the intervertebral part of the vertebral arteries (V2 segment) were also investigated by ECCD. For extracranial continuous-wave Doppler and intracranial pulsed-wave Doppler, we used the MultiDop X (DWL) with 4-, 8-, and 2-MHz probes, respectively. Extracranial and intracranial color-coded duplex sonography was performed with the Sonos 2500 system by Hewlett Packard with a 7.5-MHz linear probe and a 2.0-MHz sector probe, respectively.

We classified the stenoses taking into account the peak systolic velocity in the jet of the stenosis, broadening of the poststenotic spectrum, peak systolic velocity in the poststenotic ICA, direction of ophthalmic flow, presence of collateral flow via communicating arteries, asymmetry in pulsatility, and absolute velocity in the common carotid artery and in the middle cerebral artery (MCA). A peak systolic velocity of ≥120 cm/s was the threshold for a stenosis of ≥50%, excluding subtotal stenosis with a variable signal. In the case of indirect hemodynamic criteria, the stenosis was classified as ≥80%. Occlusion was diagnosed in the complete absence of detectable flow in and above the stenosis in the ICA and in the presence of corresponding indirect hemodynamic criteria. Plaques with stenosis <50% were classified according to their lumen reduction on B-mode ultrasonography.[17–19]

There were 6 women and 9 men aged 36 to 76 years (mean 65 years). There were 4 smokers and 1 diabetic patient. Nine individuals were hypertensive, and 7 had hyperlipidemia. Ten patients had suffered a stroke and 1 patient had a transient ischemic attack (TIA) on the side of the carotid artery under investigation up to 884 days before the investigation. Three patients had recurrent ipsilateral events, 3 had a contralateral event, and 1 had an event in the vertebrobasilar circulation. From the corresponding clinical presentation and their ultrasound appearance, all the lesions were presumed to be atherosclerotic in nature.

The original and echocontrast-enhanced investigations were continuously recorded on videotape for offline analysis. Important images were also printed out.

One 4-g vial of the echo-enhancer Levovist was applied in a concentration of 400 mg/mL by a pump injector (P400 anesthesia syringe pump, Ivac Medical Systems) at a rate of 2.5 mL/min.

The possible diagnostic benefit of the investigation was assessed immediately after the examination. The tapes were then subjected to an offline analysis that included assessment of the following parameters for both precontrast and postcontrast conditions: peak systolic blood flow velocity in the maximum stenosis; length of the color-coded blood flow column in 4 segments, each 1 cm in length starting from the flow divider; and the possibility of recording a Doppler spectrum in ≥1 location within these segments.

Six patients with 8 investigated arteries underwent intra-arterial digital subtraction angiography of their carotid arteries in close temporal relationship to the ultrasound investigation. In 1 patient, CT angiography was performed, and in another patient with 2 arteries under investigation, MR angiography was performed.

The nonparametric Friedman ANOVA was performed to test the effect of echocontrast enhancement on the length of the color column in each of the 4 segments and the possibility of recording a pulsed-wave Doppler spectrum in each of the 4 segments.

Results

The investigations did not cause any side effects. There were 8 ICA occlusions and 9 high-grade stenoses on ultrasound. Figure 1 demonstrates the ECCD findings of the left carotid artery of patient 10. Before contrast was applied, only a normal peak systolic flow velocity (91 cm/s) was obtained.

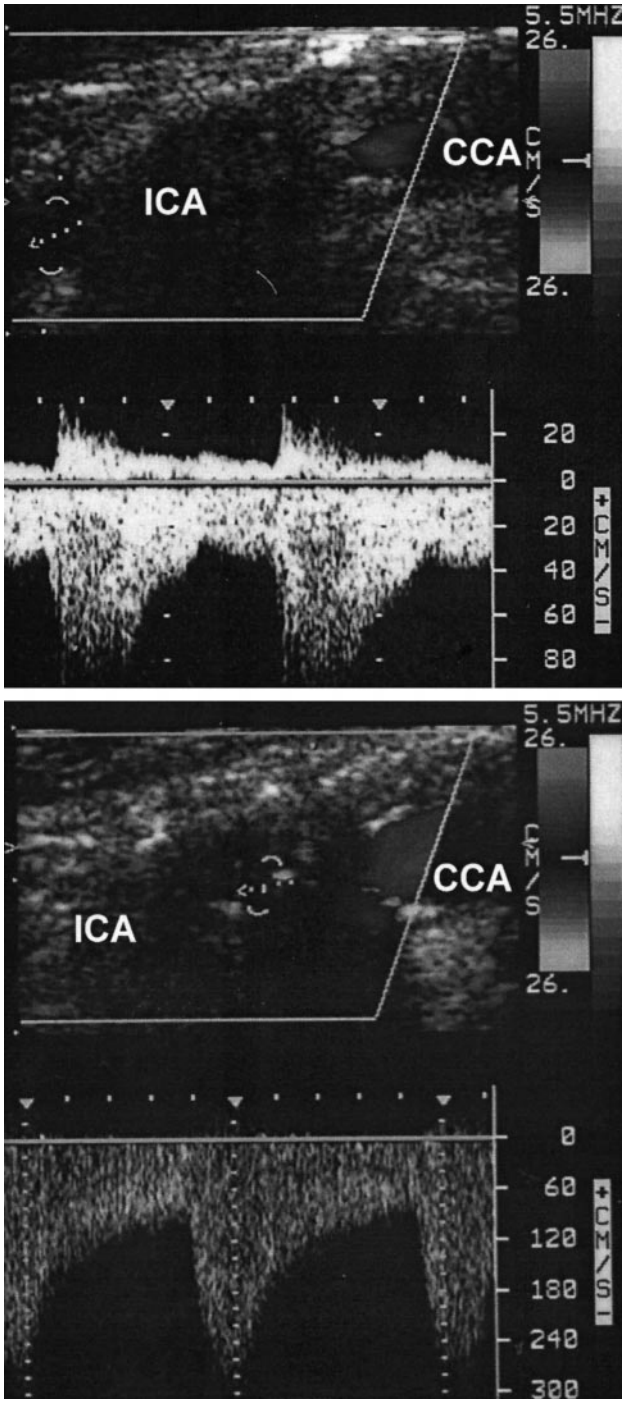

Figure 1. Left ICA of patient 10 with high-grade stenosis. Below the B-mode scans are the corresponding pulsed-wave Doppler spectra. In the precontrast investigation (upper templates), only a poststenotic signal, not an intrastenotic Doppler spectrum or a color-coded Doppler flow signal, can be recorded. The echocontrast investigation allowed the identification of part of the residual lumen in the stenosed ICA. The pathologically high flow velocity in the enhanced investigation within the stenosis (lower templates) helps to quantify the stenosis. Note the different scales on the *y* axes of the Doppler spectra. CCA indicates common carotid artery.

The maximum stenosis was presumed to be close to the sample volume; however, due to shadowing, it could not be visualized. Even after contrast application, there was no continuous visualization of the color-coded blood stream, but

Summary of Precontrast and Postcontrast ECCD Findings and Angiography (if Performed)

Patient	Side	Precontrast Result and Reason for Contrast Application	Postcontrast Results	Angiography Results
1	Right	Occlusion or subtotal stenosis?	Occlusion	(DSA) Occlusion
2	Left	Degree of stenosis? Peak systolic velocity 490 cm/s	Peak systolic velocity 495 cm/s, 95% stenosis	(DSA) 95% Stenosis
2	Right	Occlusion or subtotal stenosis?	Occlusion	(DSA) Occlusion
3	Right	Occlusion or subtotal stenosis?	Occlusion	. . .
4	Left	Degree of stenosis? Peak systolic velocity 199 cm/s	Peak systolic velocity 281 cm/s, 75% stenosis	(DSA) Filiform stenosis
5	Left	Degree of stenosis? Peak systolic velocity 170 cm/s	Recanalization of an occlusion by a vas vasorum suspected, peak systolic velocity 261 cm/s	(CTA) Vas vasorum without connection to distal ICA
6	Left	Degree of stenosis? Peak systolic velocity 69 cm/s	Peak systolic velocity 224 cm/s, 95% stenosis	(DSA) Filiform stenosis
7	Right	Occlusion or subtotal stenosis?	Occlusion	(DSA) Occlusion
8	Right	Occlusion or subtotal stenosis?	Occlusion	(DSA) Occlusion
9	Right	Degree of stenosis? Peak systolic velocity 370 cm/s	Peak systolic velocity 425 cm/s, 95% stenosis	. . .
10	Left	Degree of stenosis? Peak systolic velocity 91 cm/s	Peak systolic velocity 298 cm/s, 80% stenosis	(MRA) High-grade stenosis
10	Right	Degree of stenosis? Peak systolic velocity 80 cm/s	Peak systolic velocity 388 cm/s, 95% stenosis	(MRA) High-grade stenosis
11	Left	Occlusion or subtotal stenosis?	Occlusion	. . .
12	Left	Degree of stenosis? Peak systolic velocity 214 cm/s	Peak systolic velocity 300 cm/s, 75% stenosis	(MRA) 80% Stenosis
13	Right	Degree of stenosis? Peak systolic velocity 75 cm/s	Peak systolic velocity 95 cm/s, no extracranial stenosis detected, intracranial ICA stenosis diagnosed	. . .
14	Left	Occlusion or subtotal stenosis?	Occlusion	. . .
15	Right	Occlusion or subtotal stenosis?	Occlusion	(CTA) No filling proximally, only distal filling of the ICA; (DSA) subtotal stenosis

DSA indicates intra-arterial digital subtraction angiography; CTA, CT angiography; and MRA, MR angiography. Question marks indicate uncertain results.

a high velocity (298 cm/s), indicative of an 80% stenosis, was seen.

The Table summarizes patients' precontrast and postcontrast ECCD findings and also gives the results of angiography, if performed. In the first ICA segment of 1 cm in length distal to the flow divider, the mean length of the color-coded flow column was 9.4 mm with contrast versus 8.2 mm without contrast. The corresponding values for the second segment were 6.2 versus 3.3 mm, 4.3 versus 0.6 mm for the third segment , and 2.3 versus 0.6 mm for the fourth segment. The mean ranks from the Friedman 2-way ANOVA for the length of the color-coded flow column in each segment were (same order) 7.1 versus 6.4, 5.6 versus 4.1, 4.5 versus 2.5, and 3.2 versus 2.6, respectively ($P<0.001$). The corresponding values for the possibility of obtaining a pulsed-wave Doppler spectrum were (same order) 6.2 versus 5.9, 5.7 versus 4.7, 4.5 versus 3.3, and 3.3 versus 2.4, respectively ($P<0.001$). In the corresponding segments, all the ranks were higher for the contrast-enhanced investigation, indicating color visualization of longer parts of each segment and of more Doppler spectra with contrast than with the precontrast investigation. Figure 2 shows the benefit of contrast application for obtaining a Doppler spectrum of the different segments of the ICA.

In all but 2 of the 7 arteries (patients 4 and 15) also investigated by angiography, the ultrasound diagnosis was confirmed. In patient 15, ultrasound diagnosed an occlusion with the absence of color-coded flow and the absence of a Doppler spectrum in the course of the ICA. After the

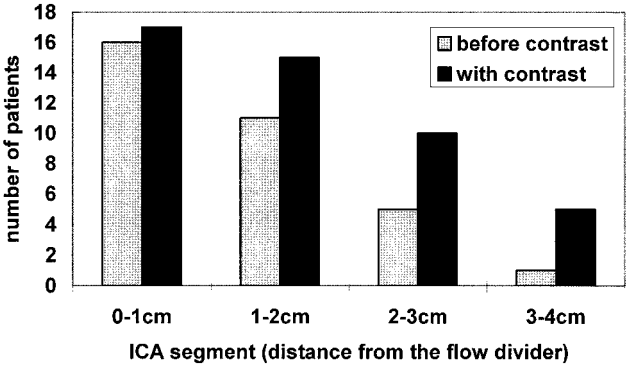

Figure 2. Possibility of obtaining a pulsed-wave Doppler spectrum in each of the 4 ICA segments. Note that there are 7 occlusions included, where in most cases, only a very short segment at the origin continued to reveal some alternating flow signal. Echocontrast helps to obtain Doppler signals, especially in the distal parts of the ICA.

ultrasound investigation, a CT angiography was performed that demonstrated no contrast enhancement in the proximal ICA but filling of the submandibular distal ICA. The patient was again taken to the ultrasound laboratory. Filling of the very distal ICA could be confirmed by echocontrast with the knowledge of the CT angiogram, but we still could not demonstrate any color-coded Doppler signal or a Doppler spectrum in the proximal ICA. Intra-arterial angiography diagnosed a subtotal stenosis, which was confirmed during subsequent endarterectomy. Figure 3 (top) shows the impossibility of detecting any flow in the proximal ICA on a longitudinal section even in the echocontrast investigation. In the bottom panel of Figure 3, the residual flow on a transverse submandibular section by echocontrast is demonstrated.

In patient 4, the degree of stenosis was underestimated by ultrasound (75%) compared with intra-arterial angiography (filiform). In patient 5, the diagnosis of recanalization of an occluded ICA by a vas vasorum was made based mainly on knowledge of the previous occlusion. An additional feature suggesting the recanalization by a vas vasorum was the uniformly narrow lumen over a segment of 1.5 cm. CT angiography confirmed a long, narrow vas vasorum that did not meet the distal ICA lumen.

Discussion

In this study, we present our experiences with echocontrast-enhanced ECCD of the carotid artery in a highly selected group of patients with difficult precontrast insonation conditions and suspected high-grade stenosis or occlusion. In most patients investigated in our neurosonological laboratory during the time period of the study, a conclusive extracranial diagnosis could be made without the use of echocontrast.

Echo enhancement enabled both the visualization of color-coded blood flow in more vessel segments and the recording of Doppler spectra in more vessel segments of the diseased artery, especially in the distal parts. Identification of the area of maximal narrowing was facilitated both for spectral and color Doppler recording. The absence of both color-coded blood flow and Doppler spectrum increased the investigator's diagnostic confidence that ICA occlusion existed. Otis et al[16] described a different condition that was not observed in our study: using contrast, they detected a still permeable tight stenosis in 4 patients with suspected occlusion. Sitzer et al[13] also described the benefit of better plaque surface characterization, an aspect that was not considered in this investigation. Furthermore, unlike in their investigation, we applied contrast only in those difficult cases in which a reliable diagnosis was not possible with the original scan.

An increase of blood flow velocity was found with the enhanced investigation used in the present study (see the Table) and has also been reported previously.[20] Several reasons may account for this finding. The contrast agent enhanced faint parts of the spectrum, which correspond to high velocities. Because the gain was downregulated if necessary during the blooming phase, this effect could only be of minor importance. In addition, the use of contrast allowed color flow and spectrum visualization in areas of the stenosis not assessable in the original scans. We applied contrast in a group of preselected patients in whom a discrepancy was found between the low maximal Doppler shift and indirect signs of an occlusive disease upstream and downstream. Visualization of the maximum stenosis thus allowed the determination of the correct maximal flow velocity and helped to quantify the stenosis.[4,5,17] True flow velocity is not altered by the application of contrast agents.[11]

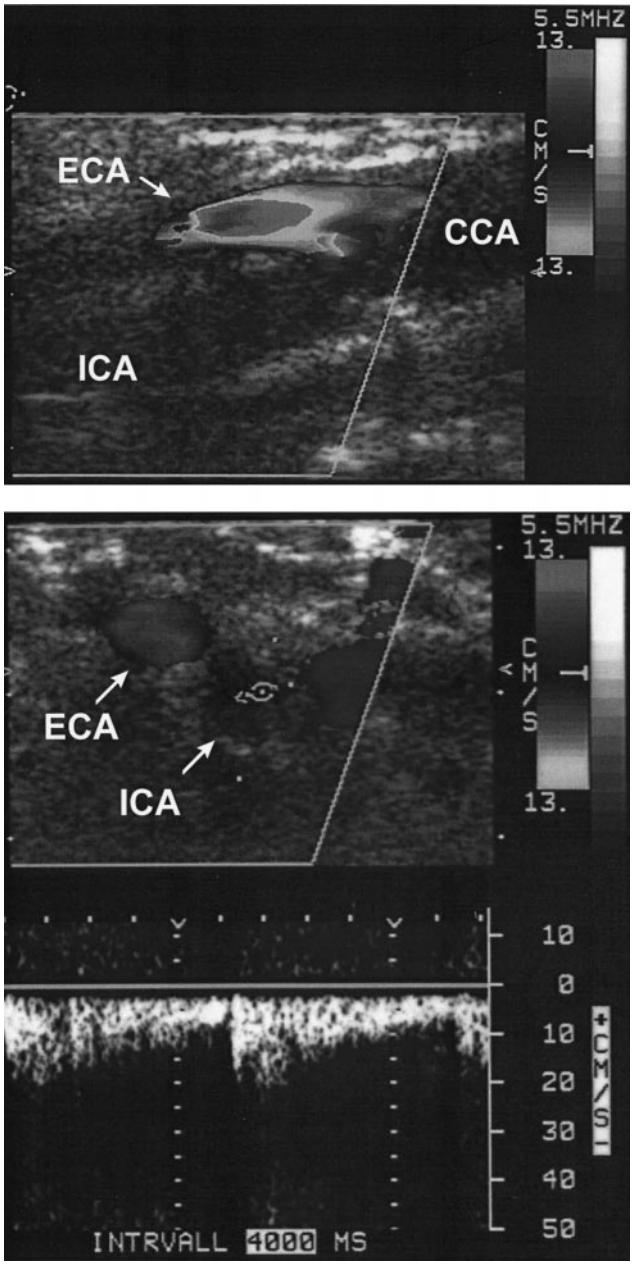

Figure 3. Patient 15. Contrast-enhanced ultrasound did not show any flow in this ICA, which was presumed to be occluded (Top, longitudinal section) but was subtotally stenosed on arteriography. After the result of a CT angiography that revealed flow in the very distal submandibular ICA, we were able to confirm this finding on a very distal submandibular transverse section using echocontrast (Bottom). This was unnoted in the first ultrasound investigation. Below the B-mode scans are the corresponding pulsed-wave Doppler spectra. CCA indicates common carotid artery; ECA, external carotid artery.

In filiform stenosis, peak systolic blood flow velocity can be low, similar to values obtained in 70% to 85% stenosis or without stenosis at all (see patient 6).[21] This was the reason

for underestimation of the degree of stenosis in patient 4. In this case, additional criteria, such as the thin color-coded flow column, B-mode ultrasonography, decreased prestenotic and poststenotic flow velocity, low pulsatility upstream and high pulsatility downstream, and pathological collateral flow, were subsidiary. Gahn et al[15] also described a similar case with a 95% to 99% stenosis underestimated as 70% to 80% on enhanced ultrasound.

In patient 5, the correct diagnosis of a recanalization of a previously occluded ICA was made with knowledge of the previous occlusion and on the basis of the long, uniformly narrow lumen.[22]

In patient 15, our ultrasound diagnosis was obviously wrong. The medial origin of the artery and deep insonation depth may have contributed to this error. Careful submandibular investigation of the ICA by echocontrast is necessary to preclude a subtotal stenosis, which may still be accessible to surgery. The lack of contrast filling in the proximal ICA on CT angiography raises the question of whether CT angiography and possibly MR angiography can serve as a reference for contrast-enhanced ultrasound studies. Intra-arterial angiography remains the "gold standard." The risk of misdiagnosing a subtotal stenosis by ultrasound is low but nevertheless exists.

Echocontrast-related side effects reported in the literature were all minor and transient.[23] Investigations like MRI, MR angiography, CT angiography, and intra-arterial angiography are potentially harmful. Of 415 patients who underwent angiography after randomization in the ACAS trial (Asymptomatic Carotid Artery Study), 3 (1.0%) suffered a disabling stroke during the investigation or between the investigation and surgery, and 1 patient died.[24] A review of 8 prospective studies[25] revealed rates of arteriography-related disabling strokes or death of 1% and 0.06% in a total of 2227 cerebral arteriographies. Moreover, MRI, MR angiography, CT angiography, and intra-arterial angiography are expensive and not yet generally available. These are additional arguments for the use of echocontrast in the ultrasound diagnosis of extracranial internal carotid artery pathology.

In summary, echocontrast agents are not only useful in intracranial color-coded duplex sonography, which still is their predominant domain, but in a small group of preselected patients, these agents were also helpful in the assessment of extracranial ICA stenoses and occlusions.

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