Usefulness of an Intravenous Contrast Medium in the Characterization of High-Grade Internal Carotid Stenosis With Color Doppler-Assisted Duplex Imaging

Matthias Sitzer, MD; Günter Fürst, MD; Mario Siebler, MD; Helmuth Steinmetz, MD

Background and Purpose The remaining limitations of ultrasonographic imaging in accurately quantifying internal carotid stenosis or diagnosing internal carotid occlusion may be overcome by enhancing the echogenicity of flowing arterial blood with contrast agents. This study assessed the usefulness of the intravenous (transpulmonary) contrast medium SH U 508 A in improving the characterization and quantification of severe internal carotid stenosis.

Methods We examined 32 patients (30 had vessels with a stenosis of greater than 70% luminal narrowing and 2 had vessel occlusions) using a 7.5-MHz linear-array transducer for color Doppler-assisted duplex imaging before and after injection of the contrast medium.

Results The SH U 508 A-induced increase in carotid blood echogenicity began 11 ± 2 (mean ± SD) seconds after the start of the bolus injection, peaked at 21 ± 2 dB, and showed a half-life of 75 seconds. Quantitative vascular measurements (cross-sectional luminal area reduction and plaque length, respectively) obtained before and after contrast application were highly correlated (r > 0.90). Visualization of the entire length of the intrastenotic residual flow lumen, however, was significantly improved by contrast enhancement (52% versus 83%, P < 0.01).

Conclusions This pilot study on patients with extracranial carotid artery disease suggested that ultrasonic contrast media may be most useful in improving the ultrasonography-based diagnosis of internal carotid occlusion. (Stroke. 1994;25:385-389.)

Key Words • carotid artery diseases • diagnostic imaging • Doppler • ultrasones

Clinical trials using invasive angiography have shown that the identification and quantification of high-grade internal carotid artery (ICA) stenosis are therapeutically relevant.1-2 Continuous-wave Doppler ultrasonography and color Doppler-assisted duplex imaging (CDDI) are capable of assessing such lesions with a high degree of accuracy.3-4 Nevertheless, the false-positive diagnosis of ICA occlusion (due to minimal residual flow) and impaired visualization of intrastenotic flow (due to calcified plaques) constitute important limitations of these noninvasive tests.3-8

Intravenous ultrasonic contrast media are known to improve the echogenicity of flowing blood.9,10 Shortcomings of these preparations have been short half-life and an inability to survive pulmonary transit.11 Two recently developed agents that overcome such disadvantages have been made available for phase III investigations. One is based on microspheres of human albumin12 and the other (used in the present study) on a saccharide microparticle suspension (code name, SH U 508 A; Schering AG). The latter agent is chemically almost identical to SH U 454 (ECHOVIST; Schering AG), differing only with respect to a minor galenic modification of the microparticles leading to improved transpulmonary intravascular stability. Intravenous application of SH U 508 A in humans is reported to opacify the left heart chambers during echocardiographic examination,13 and several ongoing trials are currently evaluating possible clinical implications of this contrast medium. In view of the aforementioned limitations of unenhanced Doppler ultrasonography, the objective of the present phase III study was to assess the usefulness of the contrast medium SH U 508 A in the characterization and quantification of high-grade ICA stenosis with CDDI.

Subjects and Methods

Patients

We examined 32 patients (14 women and 18 men; age range, 52 through 78 years; median, 64 years) with high-grade ICA stenosis (greater than 70% luminal narrowing; n = 30 vessels) or occlusion (n = 2 vessels) as determined by standard continuous-wave Doppler sonography1,2 or intra-arterial angiography.3-4 Exclusion criteria were application of an ionic contrast medium within 24 hours before or after the intended application of SH U 508 A, pregnancy or lactation, or a history of galactosemia. Written informed consent was obtained from each patient before entry into the study.

Contrast Medium

The SH U 508 A suspension contained micrometer-sized microparticles of α-D-galactose with adsorbed microscopic gaseous bubbles that acted as acoustic back-scatterers (99% of the microparticles had a diameter of less than 4 μm). One 4-g vial of granules contained 99.9% galactose microparticles and 0.1% palmitic acid. During all injections a standard 16-mL
Methods

The carotid bifurcation was insonated using a 7.5-MHz linear-array transducer (Acuson 128 XP/5) for real-time display of high-resolution B-mode gray-scale images and a 5.0-MHz pulsed-wave Doppler for superimposed simultaneous color-encoded blood flow information (CDDI). Each examination cycle included sequential longitudinal and transverse views of the affected ICA segment before and after the intravenous bolus injection of SH U 508 A. We assessed percentage of cross-sectional luminal area reduction on transverse views at the narrowest part of the stenosis and visualized the residual flow lumen in its entire length on longitudinal views (yes/no), maximal plaque length on longitudinal views, and plaque surface echomorphology (irregular surface: yes/no; ulcerative surface: yes/no). Plaque surface irregularity was defined as "blue flow" at the plaque surface; plaque surface ulceration was defined as blue flow within plaque niches. Image quality was judged as insufficient if one of these five parameters could not be determined. Twelve patients received a third injection in order to quantify the enhancement characteristics of arterial blood echogenicity after intravenous injection of SH U 508 A. For this purpose continuous blood flow velocity spectra were obtained from the ipsilateral common carotid artery with a pulsed-wave 4-MHz Doppler device (TC-2000S, EME). All CDDI evaluations were performed off-line (video documentation) by one observer (M.S.).

Investigations performed before and after the administration of SH U 508 A included neurological examination, blood pressure, serum hemoglobin, red blood cell count, mean corpuscular volume, total and differential leukocyte count, platelet count, alkaline phosphatase, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, glutamyl-transpeptidase, lactate dehydrogenase, hydroxybutyrate dehydrogenase, amylase, lipase, creatine phosphokinase, creatine phosphokinase MB isoenzyme, creatinine, blood urea nitrogen, total bilirubin, sodium, potassium, total protein, and albumin; and urinalysis, including total protein, albumin, and y-glutamyltranspeptidase.

Statistical Analysis

Nonenhanced and enhanced findings were compared with chi-squared tests for categorical data and linear or nonlinear regression analyses for continuous data. Probability values of less than .05 were considered significant. Data are expressed as mean ± SD unless otherwise noted.

Results

Blood Flow Echogenicity

The influence of intravenously injected SH U 508 A on carotid blood flow echogenicity is shown in Figs 1 and 2, which illustrate the magnitude, frequency distribution, and time course of the increase in reflected ultrasonic energy. The three-dimensional plot of Fig 1 exemplifies the enhancement of the entire blood flow velocity spectrum observed after bolus injection, corresponding to a maximum increase in reflected energy of almost 18 dB compared with precontrast values. The plot also shows the typical increase of the arterial peak flow velocity due to the augmentation of rare high-velocity components, which remain below the sensitivity threshold without contrast enhancement. The time course of arterial enhancement averaged across 12 patients is shown in Fig 2. The increase in blood echogenicity began 11 ± 2 seconds after the start of the bolus injection and reached a maximum of 21 ± 2 dB.

Echomorphology of High-Grade ICA Stenoses

<table>
<thead>
<tr>
<th></th>
<th>Nonenhanced</th>
<th>Enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular plaque surface</td>
<td>22/25 (88%)</td>
<td>29/30 (97%)</td>
</tr>
<tr>
<td>Ulcerative plaque surface</td>
<td>6/25 (24%)</td>
<td>12/30 (40%)</td>
</tr>
<tr>
<td>Image quality insufficient</td>
<td>7/32 (21%)</td>
<td>2/32 (6%)</td>
</tr>
<tr>
<td>Visualization of entire residual lumen</td>
<td>13/25 (52%)</td>
<td>25/30 (83%)</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; nonenhanced and enhanced refer to color Doppler-assisted duplex imaging. Views are longitudinal; numbers indicate numbers of vessels. For echomorphological criteria, see "Methods."
after 15±3 seconds. The subsequent decrease in carotid blood echogenicity followed an exponential decay, with a half-life of 75.3 seconds (τ=108.7 seconds; see Fig 2 inset). The systolic peak-flow velocity rose by 26.0±9% (P<.05) averaged across these 12 individuals.

**Degree of Stenosis and Plaque Morphology**

The Table shows that the yield of interpretable data was higher under contrast-enhanced conditions, with image quality being judged as sufficient in 30 of 32 ICAs (94%) compared with 79% before contrast application (P=.07). The plaque surface was considered irregular in 97% of ICAs studied after contrast enhancement (87% precontrast; P=.21). Plaque ulceration was diagnosed in 40% on enhanced CDDI (24% precontrast; P=.21). For the quantitative CDDI parameters, high correlations were found between enhanced and nonenhanced measurements (r=.90 for cross-sectional luminal narrowing and r=.94 for plaque length).

**Residual Flow Lumen**

A significant difference between nonenhanced and enhanced CDDI was found for the visualization of the entire length of the intrastenotic residual flow lumen on longitudinal views (52% precontrast, 83% postcontrast; P=.01; Fig 3). In the two cases of angiographically proven carotid occlusion, no residual flow signal was found in the affected ICA segment.
Discussion

The evaluation of high-grade ICA stenosis with CDDI is often hampered by plaque calcification, very narrow residual lumina, or increased absorption of ultrasonic energy by heterogeneous atherosclerotic wall components. Thus, previous authors have noted unsatisfactory imaging conditions in 15% to 29% of patients examined with conventional duplex imaging15-17 and in 8% to 13% using CDDI.4,6,8 One result of the present CDDI study on 32 high-grade ICA lesions was that an intravenous contrast agent reduced the percentage of uninterpretable cases from 21% before to 6% after contrast application (P=.07). In patients with sufficient precontrast image quality, however, the use of SH U 508 A did not significantly improve the echomorphological characterization of the plaque surface (Table) or the quantification of the degree of high-grade ICA stenosis.

The contrast agent used in our investigation was clinically easy to handle, and its application was not associated with observable side effects. The increase in blood flow echogenicity was considerable (mean, 21 dB) and lasted more than 3 minutes after each injection (Fig 2), thereby providing time for detailed CDDI evaluations. Together with the observed intensity augmentation (Fig 1), this explains what we consider the most important finding of our study, i.e., the significantly improved visualization of the residual intrastenotic flow lumen in its entire length (Table and Fig 3).

Physically, conventional CDDI devices are known to fail in the detection of the fastest (central jet) and slowest components of the quasi-parabolic velocity profile because of below-threshold intensity of reflected energies under nonenhanced conditions.18,19 Due to global intensity augmentation after the application of a contrast medium, a broadening of the visualized velocity spectrum had to be expected and was indeed observed in the present study. This led to a 26% increase in the measured systolic peak-flow velocity (Fig 1). In addition, and even more important, enhancement of the slowest velocity components was also considerable (Fig 1, inset). This explains the higher percentages of irregular and ulcerative plaques observed after contrast application (Table), because these designations were solely based on the presence of turbulences at the plaque surface (Fig 3) or within plaque niches. Such findings cast further doubt on the validity of these echomorphological designations,8 at least in high-grade carotid lesions.

Clinically, the most relevant pitfall of neurosonography has always been the diagnosis of ICA occlusion, with percentages of false-positives ranging between 5% and 62% in reported series.5,15,20,21 Compared with continuous-wave Doppler sonography and conventional duplex B-mode imaging, nonenhanced CDDI has already improved the sensitivity for detecting minimal residual blood flow in preocclusive conditions.4,8,22 Our data suggest that enhanced CDDI may go one step further by being capable of detecting flow even within the narrowest parts of high-grade stenoses and in the poststenotic slow-flow segment, where flow signal intensities may be below the detection thresholds of nonenhanced CDDI (Fig 3). This particular strength of enhanced CDDI may also be demonstrated by the findings in one patient of the present sample whom we diagnosed to be suffering from (symptomatic) ICA occlusion on both continuous-wave Doppler and nonenhanced CDDI examinations. Nevertheless, enhanced CDDI conducted on the same day showed a strand of residual blood flow (Fig 4). On intra-arterial angiography performed 36 hours later, the typical finding of an atheromatous pseudo-occlusion23-27 was confirmed, and the patient's ICA was successfully revascularized soon afterward. We concluded from the data of this pilot study that the differentiation between occlusive and preocclusive ICA lesions is likely to constitute the most relevant clinical indication for the use of ultrasonic contrast media in patients with extracranial carotid disease.

Acknowledgments

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