Color-flow Doppler-assisted duplex imaging fails to detect ulceration in high-grade internal carotid artery stenosis

Matthias Sitzer, MD, Wolfram Müller, MD, Jörg Rademacher, MD, Mario Siebler, MD, Waldemar Hort, MD, H.-W. Kniemeyer, MD, and **Helmuth Steinmetz, MD,** *Düsseldorf, Germany*

Purpose: **Pathoanatomic studies suggest that plaque surface disruption, particularly ulceration, plays a key role in the destabilization of internal carotid artery stenosis. Until now, the validity of color-flow Doppler-assisted duplex imaging in detecting such pathoanatomically defined plaque surface abnormalities is unclear.**

Methods: **We prospectively determined the interobserver reliability and validity of detecting plaque ulceration by means of preoperative color-flow Doppler-assisted duplex imaging in 43 consecutive patients with high-grade (≥ 70%) internal carotid artery stenosis, comparing these ultrasonographic findings with pathoanatomic evaluations of the corresponding endarterectomy specimens.**

Results: **Interobserver reliabilities for detecting carotid plaque ulceration were $\kappa = 0.57$ for ultrasonography and $\kappa = 0.82$ for the pathologic reference method. Color-flow Doppler-assisted duplex imaging (observer consensus) failed to detect pathoanatomically defined ulceration ($\chi^2 = 0.43$; $p = 0.51$). Likewise, sensitivity, specificity, overall accuracy, and positive predictive value were poor (33%, 67%, 56%, and 46%, respectively).**

Conclusions: **We conclude from our data that color-flow Doppler-assisted duplex imaging is not a reliable or valid means to identify plaque ulceration in high-grade carotid artery lesions. (J VASC SURG 1996;23:461-5.)**

Several pathohistologic investigations have provided evidence that the disruption of internal carotid artery (ICA) atherosclerotic plaques eventually leading to plaque ulceration and intraluminal thrombosis is the key event in converting asymptomatic into symptomatic ICA lesions.[1-5] Thus the early or even presymptomatic detection of plaque surface disruption, especially plaque ulceration, may be of prognostic and therapeutic relevance.

Reliable detection of plaque surface abnormalities is a sine qua non for studying their natural history. High-resolution B-mode ultrasonography and, more recently, color-flow Doppler-assisted duplex imaging (CDDI) have been proposed as suitable means of studying plaque morphology, because of the combination of B-mode imaging and superimposed blood flow velocity information.[6] Previous authors have also suggested that ultrasonographic ulceration may be more frequent in patients having recently had transient retinal or cerebral symptoms or minor stroke,[7-10] and that the identification of plaque ulceration may per se justify carotid endarterectomy. However, pathohistologic validation of the CDDI-based diagnosis of ICA "plaque ulceration" is lacking. The purpose of our study was to determine the interobserver reliability and validity of CDDI in detecting pathologically defined plaque ulceration in high-grade ICA stenosis.

From the Departments of Neurology, Pathology (Drs. Müller and Hort), and Vascular Surgery and Renal Transplantation (Dr. Kniemeyer), Heinrich-Heine-University, Düsseldorf.

Supported by grants from the Deutsche Forschungsgemeinschaft (Si 370/4-1) and the Hermann-und-Lilly-Schilling-Stiftung (H.S.).

Reprint requests: Helmuth Steinmetz, MD, Department of Neurology, Heinrich-Heine-University, Moorenstrasse 5, PO Box 101007, D-40001 Düsseldorf, Germany.

0741-5214/96/$5.00 + 0 **24/1/68215**

PATIENTS AND METHODS

Patients. This study prospectively included 43 consecutive inpatients (14 women and 29 men; age range, 41 to 84 years; median, 61 years) enlisted to undergo carotid endarterectomy for extracranial high-grade ICA stenosis (≥ 70% luminal narrowing) as determined by cervical ultrasonography.[11] Of them, 30 patients were classified as having symptoms

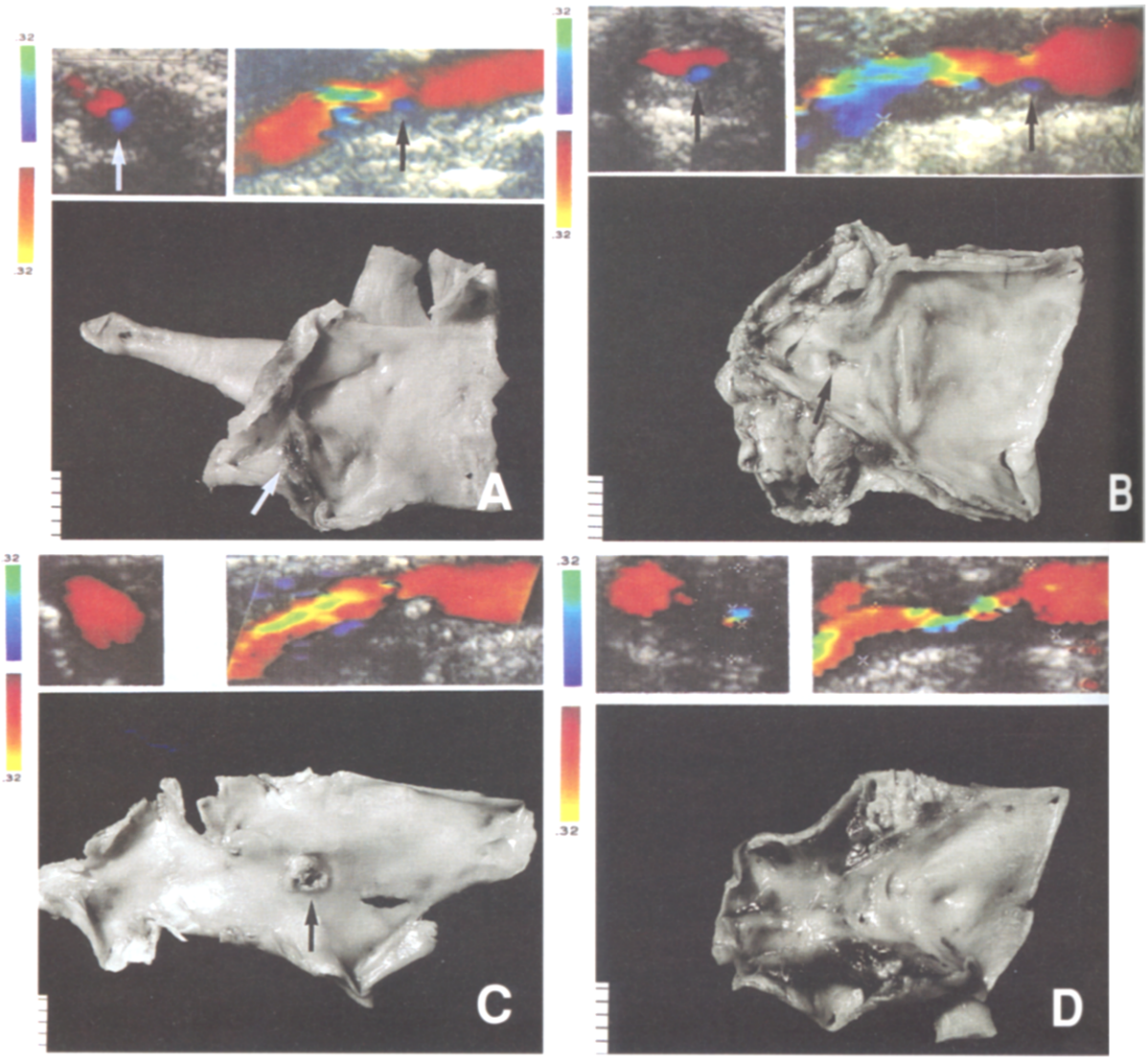

Fig. 1. CDDI of ICA stenosis and corresponding photographs of carotid endarterectomy specimens obtained from four patients with ultrasonographic or pathoanatomic ulceration. Transverse and longitudinal CDDI sections are displayed for each case in which blood flow away from transducer is coded in red, toward transducer in blue, and aliasing phenomena in green; ends of color scale indicate mean blood flow velocities of 0.32 m/sec. In each figure proximal end of vessel/specimen is to *right*. Scaling is same for CDDI and pathoanatomic photographs, with distances between *vertical bars* in each figure indicating 1 mm. **A,** CDDI reveals ulceration at proximal part of ICA plaque *(arrow)*, confirmed by pathologic analysis (*arrow*, "true positive"). **B,** CDDI reveals ulceration at proximal part of ICA plaque *(arrow)*, whereas pathologic study shows plaque irregularity without surface defect (*arrow*, "false positive"). **C,** CDDI shows no ulceration on perpendicular sections, whereas pathologically plaque ulceration is clearly present (*arrow*, "false negative"). **D,** CDDI reveals no ulceration, confirmed by pathologic analysis showing minor irregularities without surface defects ("true negative").

because they had recently (less than 121 days before enlistment) had transient retinal or cerebral symptoms or a minor ischemic stroke attributable to the ICA lesion.[12] The remaining 13 patients were considered to be symptom free because they had a history of no or only remote (more than 120 days before enlistment) ischemic symptoms. Informed consent was obtained from all patients before each examination.

Ultrasonographic examinations. The interval between CDDI examination and carotid endarterectomy was 1 to 21 days (median, 4.5 days; mean, 5.3 ± 1.9 [SD] days). The carotid bifurcation was

Table I. Relationships between ultrasonographic features and pathoanatomic plaque ulceration in 39 high-grade internal carotid artery stenoses/specimens

	Pathoanatomic ulceration		
	Absent (n/%) (n = 21)	*Present (n = 18)*	*p*
Plaque surface echomorphology (CDDI)			
Ulceration	5/24	6/33	0.51
Irregular	9/43	11/61	0.26
Smooth	7/33	1/6	0.03
Plaque tissue echomorphology (B-mode)			
Heterogeneous	10/48	11/61	0.39
Homogeneous	11/52	7/39	0.39
Calcified	8/38	7/38	0.96

Numbers indicate numbers of vessels/specimens; % indicates percentages of group.

insonated with a 7.5 MHz linear-array transducer (model 128 XP/5; Acuson Inc., Mountain View, Calif.) 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 (anterooblique/posterooblique/lateral) and transverse views of the entire atherosclerotic ICA plaque. Blood flow away from the transducer was coded in red, blood flow toward the transducer in blue, and aliasing phenomena in green (Fig. 1). Image quality was judged as insufficient if the residual intrastenotic flow lumen was not visualized in its entire length on both longitudinal and transverse views. All CDDI evaluations were performed off-line (video documentation: S-VHS recorder, AG-7350; Matsushita Electric, Osaka, Japan) by two independent observers blinded for individual clinical and pathoanatomic data.

Ultrasonographic plaque ulceration was defined as a plaque niche filled with reversed slow flow on longitudinal views, found at the same location on transverse views, without evidence of aliasing phenomena (Fig. 1, *A* and *B*). In the absence of ulceration, plaque surface was characterized as smooth or irregular.[9] Interobserver reliability for detecting plaque ulceration was $\kappa = 0.57$ for this sample. The prevalence of ultrasonographic plaque ulceration reported in the following is based on the consensus achieved between both observers at joint reevaluation of their data previously obtained independently. In addition, plaque tissue echomorphology as visible on B-mode images was characterized as heterogeneous (mixed low-/medium-/high-level echos), homogeneous (uniform echo level), or calcified (acoustic shadowing).[9]

Pathoanatomic examinations. After longitudinal arteriotomy, the carotid atherosclerotic plaque was excised en bloc by the vascular surgeon (routine endarterectomy). The fresh specimen was rinsed briefly in normal saline solution to remove surface blood. It was then fixed immediately in 4% paraformaldehyde solution, and a gross photograph was taken on which areas of particular interest were marked by a pathologist for consecutive sectioning. After decalcification, the entire specimen was sectioned transversely into 2 mm thick slices starting proximally. After embedding the slices in paraffin, three or four 5 μm sections were obtained from each slice and stained with hematoxylin and eosin and Van Gieson's stain.

Gross visual inspection and histologic examinations were performed independently by two pathologists blinded for individual clinical and ultrasonographic data. Pathoanatomic plaque ulceration was defined as a surface defect larger than 1 mm in width, exposing the necrotic core of the atheromatous plaque. Interobserver reliability for detecting so-defined plaque ulceration was $\kappa = 0.82$ for this sample. The prevalence of pathoanatomic plaque ulceration reported in the following is based on the consensus achieved between both pathologists at joint reevaluation of their data previously obtained independently.

Statistical analysis. With κ statistics the reliabilities between both ultrasonographic observers and both pathologists for detecting the aforementioned ultrasonographic or pathoanatomic abnormalities were calculated from their independent evaluations of the entire sample (values given above), respectively. The validity of CDDI in detecting plaque ulceration was analyzed by χ^2 statistics. A significance level of $p = 0.05$ was chosen. In addition, the sensitivity, specificity, overall accuracy, and predictive values for a CDDI-based diagnosis of ICA plaque ulceration were determined. Degrees of stenosis were compared with the unpaired Student *t* test.

Table II. Specificity, sensitivity, predictive values, and overall accuracy of preoperative CDDI for detecting plaque ulcerations in 39 high-grade ICA stenoses (reference method: pathoanatomic evaluation of corresponding carotid endarterectomy specimens)

	CDDI	
	%	*n*
Specificity	0.76	16/21
Sensitivity	0.33	6/18
Positive predictive value	0.54	6/11
Negative predictive value	0.57	16/28
Overall accuracy	0.56	22/39
Prevalence	0.46	18/39

Numbers are numbers of vessels/specimens.

RESULTS

Four patients were excluded from the analysis because of insufficient CDDI image quality (n = 3; 7%) or severe plaque distortion caused by the endarterectomy procedure (n = 1; 2%). Among the remaining 39 vessels/specimens, ultrasonographic plaque ulceration was found in 11 ICAs (28%), whereas pathoanatomic plaque ulceration occurred in 18 specimens (46%). The mean degree of ICA stenosis did not differ between patients with (84% ± 7.5% [SD]) and without (82% ± 11.0% [SD]; $p = 0.66$) pathoanatomic plaque ulceration. The mean maximum widths of ultrasonographic and pathoanatomic plaque ulcerations were 3.5 ± 1.3 (SD) mm and 3.8 ± 2.1 (SD) mm, respectively. Pathoanatomically, the vast majority of ulcers were described as flat. The relationships between ultrasonographic features and pathoanatomic plaque ulceration are given in Table I. The only significant finding was an inverse relationship between smooth plaque surface on CDDI and pathoanatomic ulceration ($p = 0.03$). The sensitivity, specificity, overall accuracy, and predictive values for ultrasonographic plaque ulceration are given in Table II, indicating the failure of CDDI to detect ICA plaque ulceration.

DISCUSSION

Depending on the diagnostic method, different criteria have been used for identifying atherosclerotic ICA plaque ulceration. Pathoanatomically, such ulcers have been defined as plaque surface defects of at least 1 mm in diameter and depth[13,14] or more than 560 μm in diameter and depth.[15] Angiographically, ulceration has been considered present if seen in profile as a crater or "double density" on en face view.[2,16-19] High-resolution B-mode ultrasonography has visualized presumed ulcers as interruptions of the plaque surface that had to be visible on at least one plane of section,[20] two planes of section,[21] or with an extension of at least 1 mm in diameter and depth.[13] With CDDI, Steinke et al.[9] defined ulceration as a niche within the ICA plaque filled with reversed flow. Our CDDI definition was similar to that of Steinke et al., with the extension that flow reversal within the niche had to be visible on at least two perpendicular planes of section and without evidence of aliasing phenomena (Fig. 1.) Nevertheless, it is conceivable that flat ulcers or those covered with thrombi[1,3,4] are missed by such criteria, and surface irregularities without intimal defects are falsely detected as ulcers. We presume that these are the main explanations for the negative result of our study. Unfortunately, the incorporation of B-mode echomorphologic features did not improve the CDDI-based diagnosis of pathoanatomic ulceration (Table I).

It deserves mention that six of the aforementioned previous studies also included comparisons of their angiographic or ultrasonographic findings with a pathoanatomic standard of reference. Compared with our data, most of them were equally disappointing. Thus sensitivities and positive predictive values for angiographic or B-mode ultrasonographic diagnoses of plaque ulceration ranged from 0.46 to 0.73 (angiographic sensitivity),[14,16-18,21] 0.39 to 0.89 (B-mode sensitivity),[13,14,21] 0.53 to 0.91 (angiographic positive predictive value),[14,16-18,21] and 0.47 to 0.84 (B-mode positive predictive value; Table II).[13,14,21] Interestingly enough, interobserver reliabilities were given by only two of these between-method investigations.[16,17] Both of them were angiographic studies and concluded that, before considering validity, angiographic ICA ulceration cannot even be diagnosed reliably enough to be a particularly promising feature.

Reliabilities for B-mode ultrasonographic diagnoses of ICA plaque ulceration were determined by two other groups who found interobserver agreements of $\kappa = 0.11$[22] and $\kappa = 0.54$.[23] Again, our equally disappointing results ($\kappa = 0.57$) fit well within this context. Thus we conclude from this study that the failure of CDDI to detect pathologically defined plaque ulceration in high-grade ICA stenosis was twofold. First, the diagnosis of ulceration made with CDDI was inaccurate even if based on observer consensus (see Table II for predictive values) and, second, reliability of the CDDI criteria was too low to encourage further studies whether the flow phenomena evaluated (pseudoulcers; Fig. 1, *A* and *B*) per

se may have prognostic implications as potential sites of thrombus or embolus formation.

We suggest that, compared with cervical ultrasonography in its present state, a better method for the noninvasive detection of ICA plaque ulceration may be the recording of plaque-derived microemboli by means of transcranial Doppler ultrasonography. Two recent studies that used this method have compared the occurrence of microemboli in the ipsilateral middle cerebral artery with findings in corresponding carotid endarterectomy specimens, and both found high predictive values with respect to plaque ulceration.[24,25]

REFERENCES

1. Hertzer NR, Beven EG, Benjamin SP. Ultramicroscopic ulcerations and thrombi of the carotid bifurcation. Arch Surg 1977;112:1394-402.
2. Moore WS, Boren C, Malone JM, et al. Natural history of nonstenotic, asymptomatic ulcerative lesions of the carotid artery. Arch Surg 1978;113:1352-9.
3. Ogata J, Masuda J, Yutani C, Yamaguchi T. Rupture of atheromatous plaque as a cause of thrombotic occlusion of stenotic internal carotid artery. Stroke 1990;21:1740-5.
4. Sterpetti AV, Hunter WJ, Schultz RD. Importance of ulceration of carotid plaque in determining symptoms of cerebral ischemia. J Cardiovasc Surg 1991;32:154-8.
5. Fisher M, Martin A, Cosgrove M, Norris J. Stroke symptoms from carotid artery plaques [abstract]. Stroke 1994;25:272.
6. Mitchell DG. Color Doppler imaging: principles, limitations, and artifacts. Radiology 1990;177:1-10.
7. Johnson JM, Ansel AL, Morgan S, DeCesare D. Ultrasonographic screening for evaluation and follow-up of carotid artery ulceration. Am J Surg 1982;144:614-8.
8. Kessler C, Maravic C, Maravic M, Koempf D. Colour Doppler flow imaging of the carotid arteries. Neuroradiology 1991; 33:114-7.
9. Steinke W, Hennerici M, Rautenberg W, Mohr JP. Symptomatic and asymptomatic high-grade carotid stenoses in Doppler color-flow imaging. Neurology 1992;42:131-8.
10. Wechsler LR. Ulceration and carotid artery disease. Stroke 1988;19:650-3.
11. Sitzer M, Fuerst G, Fischer H, et al. Between-method correlation in quantifying internal carotid stenosis. Stroke 1993;24:1513-8.
12. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Steering Committee. North American Symptomatic Carotid Surgery Trial: methods, patients characteristics, and progress. Stroke 1991;22:711-20.
13. O'Leary DH, Holen J, Ricotta JJ, Roe S, Schenk EA. Carotid bifurcation disease: prediction of ulceration with B-mode US. Radiology 1987;162:523-5.
14. Comerota AJ, Katz ML, White JV, Grosh JD. The preoperative diagnosis of the ulcerated carotid atheroma. J Vasc Surg 1990;11:505-10.
15. Fisher M, Martin A, Cosgrove M, Norris JW. The NASCET-ACAS plaque project. Stroke 1993;24(suppl):I24-5.
16. Eikelboom BC, Riles TR, Mintzer R, et al. Inaccuracy of angiography in the diagnosis of carotid ulceration. Stroke 1983;14:882-5.
17. Estol C, Claassen D, Hirsch W, Wechsler L, Moossy J. Correlative angiographic and pathologic findings in the diagnosis of ulcerated plaques in the carotid artery. Arch Neurol 1991;48:692-4.
18. Streifler JY, Eliasziw M, Fox AJ, et al, for the North American Symptomatic Carotid Endarterectomy Trial. Angiographic detection of carotid plaque ulceration: comparison with surgical observations in a multicenter study. Stroke 1994;25: 1130-2.
19. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJM, for the North American Symptomatic Carotid Endarterectomy Trial. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. Stroke 1994;25:304-8.
20. Zwiebel WJ, Austin CW, Sackett JF, Strother CM. Correlation of high-resolution, B-mode and continuous-wave Doppler sonography with arteriography in the diagnosis of carotid stenosis. Radiology 1983;149:523-32.
21. O'Donnell TF, Erdoes L, Mackey WC, et al. Correlation of B-mode ultrasound imaging and arteriography with pathologic findings at carotid endarterectomy. Arch Surg 1985; 120:443-9.
22. O'Leary DH, Bryan FA, Goodison MW, et al. Measurement variability of carotid atherosclerosis: real-time (B-mode) ultrasonography and angiography. Stroke 1987;18:1011-7.
23. Anderson DC, Loewenson R, Yock D, Farber R, Larson D, Bromer M. B-mode, real-time carotid ultrasonic imaging: correlation with angiography. Arch Neurol 1983;40:484-8.
24. Spencer MP. Doppler microembolic signals for diagnosis of ulcerated carotid artery plaques [abstract]. Stroke 1995;26: 732.
25. Sitzer M, Müller W, Siebler M, et al. Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. Stroke 1995; 26:1231-3.

Submitted Jan. 16, 1995; accepted July 28, 1995.