# Hemispheric symptoms and carotid plaque echomorphology

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*Purpose:* **In patients with carotid bifurcation disease, the risk of stroke mainly depends on the severity of the stenosis, the presenting hemispheric symptom, and, as recently suggested, on plaque echodensity. We tested the hypothesis that asymptomatic carotid plaques and plaques of patients who present with different hemispheric symptoms are related to different plaque structure in terms of echodensity and the degree of stenosis.**
*Methods:* **Two hundred sixty-four patients with 295 carotid bifurcation plaques (146 symptomatic, 149 asymptomatic) causing more than 50% stenosis were examined with duplex scanning. Thirty-six plaques were associated with amaurosis fugax (AF), 68 plaques were associated with transient ischemic attacks (TIAs), and 42 plaques were associated with stroke. B-mode images were digitized and normalized using linear scaling and two reference points, blood and adventitia. The gray scale median (GSM) of blood was set to 0, and the GSM of the adventitia was set to 190 (gray scale range, black = 0; white = 255). The GSM of the plaque in the normalized image was used as the objective measurement of echodensity.**
*Results:* **The mean GSM and the mean degree of stenosis, with 95% confidence intervals, for plaques associated with hemispheric symptoms were 13.3 (10.6 to 16) and 80.5 (78.3 to 82.7), respectively; and for asymptomatic plaques, the mean GSM and the mean degree of stenosis were 30.5 (26.2 to 34.7) and 72.2 (69.8 to 74.5), respectively. Furthermore, in plaques related to AF, the mean GSM and the mean degree of stenosis were 7.4 (1.9 to 12.9) and 85.6 (82 to 89.2), respectively; in those related to TIA, the mean GSM and the mean degree of stenosis were 14.9 (11.2 to 18.6) and 79.3 (76.1 to 82.4), respectively; and in those related to stroke, the mean GSM and the mean degree of stenosis were 15.8 (10.2 to 21.3) and 78.1 (73.4 to 82.8), respectively.**
*Conclusion:* **Plaques associated with hemispheric symptoms are more hypoechoic and more stenotic than those associated with no symptoms. Plaques associated with AF are more hypoechoic and more stenotic than those associated with TIA or stroke or those without symptoms. Plaques causing TIA and stroke have the same echodensity and the same degree of stenosis. These findings confirm previous suggestions that hypoechoic plaques are more likely to be symptomatic than hyperechoic ones. They support the hypothesis that the pathophysiologic mechanism for AF is different from that for TIA and stroke. (J Vasc Surg 2000;31:39-49.)**

In patients with symptomatic carotid bifurcation disease, the severity of internal carotid artery stenosis is the main criterion used to determine the risk of stroke.[1,2] Several investigators have shown that hypoechoic plaques are associated with a higher incidence of hemispheric symptoms, and ipsilateral computed tomography-brain infarcts than hyperechoic ones.[3-10] It has been suggested that hypoechoic, lipid-rich plaques are associated with an increased risk because they are vulnerable to rupture, which contributes to the development of symptoms.[11-14] However, some investigators consider the prognosis of patients with amaurosis fugax (AF) to be favorable in comparison with that of patients with hemi-

**Fig 1.** Hypoechoic plaque (*outlined*) with the near and far wall common carotid artery adventitia of similar brightness and the time-gain compensation curve gently sloping but vertical through the vessel lumen (*arrowheads*).

spheric transient ischemic attacks (TIAs).[15,16] This finding may be the result of a different pathophysiologic mechanism.

The aim of this study was to determine the differences, if any, in the echodensity and the degree of stenosis of carotid plaques in asymptomatic patients and in those patients presenting with different hemispheric symptoms. Our hypothesis was that different presenting symptoms may be attributed to differences in plaque structure and the degree of stenosis.

## METHODS

**Patients.** For the purposes of this cross-sectional study, 264 patients (186 men and 78 women) with 295 carotid bifurcation plaques causing 50% to 99% diameter stenosis were studied with high resolution ultrasound. One hundred forty-six plaques were related to symptomatic hemispheres, and 149 plaques were related to asymptomatic hemispheres. Thirty-six plaques were associated with AF, 68 plaques were associated with TIA, and 42 plaques were associated with stroke.

All patients had been examined by a neurologist to determine whether they were symptomatic. Patients with atrial fibrillation, valvular lesions, or previous cerebral hemorrhage were excluded.

**Carotid duplex settings.** All the ultrasound scans were performed with the ATL HDI 3000 (Advanced Technologies Laboratories, Seattle, Wash) duplex scanner with a 7-4-MHz multifrequency linear array probe. The degree of stenosis was evaluated by using

the ratio of the peak systolic velocity of the internal carotid artery to the peak systolic velocity of the common carotid artery, based on previous validation studies,[17,18] and the ratio of the peak systolic velocity of the internal carotid artery to the end diastolic velocity of the common carotid artery.[19] The latter ratio has been correlated in our vascular laboratory with angiographic stenosis in relation to the distal internal carotid artery. This has enabled us to grade carotid stenosis greater than 50% by means of duplex scanning, with an error rate of plus or minus 7%.[20,21] Because absolute velocities at the level of the stenosis can be affected by a number of circulatory conditions unrelated to the carotid artery lesions, such as cardiac arrhythmia, aortic valve disease, tandem plaques, and contralateral carotid artery occlusion, the two velocity ratios were used, rather than the absolute velocity measurements.[22,23]

B-mode settings were adjusted so that the maximum dynamic range (60 dB) and a linear postprocessing curve were used. By using the full dynamic range, the maximum number of gray levels was available. Because normalization of the B-mode images is achieved by using linear scaling of the original image obtained by the duplex scan, images should not be subjected to the postprocessing curves available to many duplex machines, which are not as close to linear as possible. The ultrasonic beam was at right angles to the arterial wall. Ultrasonic scanning images are the result of reflections from tissue interfaces. Because adventitia is a key reference point in the normalization

process, the optimum image was provided only when the ultrasonic beam was at right angles to it. Although the time-gain compensation curve should be gently sloping so that the gray tones of tissues are not attenuated despite depth, it should be vertical through blood. Because blood causes little attenuation of ultrasound, the near and far wall adventitia were ensured to be of similar brightness (Fig 1). The overall gain was set so that areas of blood (vessel lumen) were free of noise. The application of these prerequisites ensured the availability of the two reference points for normalization of the B-mode images, blood (black) and adventitia (white).

**Carotid plaque image acquisition and normalization.** During carotid plaque scanning, optimum image magnification was ensured so that the whole plaque was included in the image, with a clearly visualized section of adventitia in its vicinity. Once the best available image of the carotid plaque was identified, it was directly digitized on a magneto-optical disk or recorded on video, and the still image was digitized off-line on a personal computer with a commercially available video-grabber card. The corresponding colored image was also digitized, an essential requirement for outlining hypoechoic plaques or those plaques that are heterogenous, with their hypoechoic component adjacent to the lumen of the vessel. Plaques for which we did not have any B-mode information because of acoustic shadowing were excluded from the study.

By means of Adobe Photoshop (version 3.0) software, the digitized images were normalized off-line by using linear scaling and two reference points, blood and adventitia. The gray scale median (GSM) of blood was set to 0 to 5, and the GSM of the adventitia to 185 to 195 (gray scale range, 0 to 255; black = 0, white = 255). The median of the gray tone frequency distribution of the pixels in the plaque (GSM) in the normalized image was used as the objective measurement of the echodensity. Because this distribution is usually skewed, the median, rather than the mean, is used for all measurements. (Figs 2 and 3). The gray tone frequency distribution of the pixels in the plaque is provided by the "histogram" facility of Adobe Photoshop, and the image is normalized by performing linear scaling with the "curves" facility. These two features provided by this particular software are essential for B-mode image normalization and plaque characterization by means of GSM. The observer who normalized the carotid plaque images was blinded to the clinical information and the degree of stenosis. The reproducibility of this method has been previously reported.[24]

**Statistical analysis.** The different groups of patients (those patients presenting with AF, TIA, or stroke and those patients without symptoms) were tested for normality with the Kolmogorov-Smirnov test and the Levene test for the homogeneity of variances. Subsequently, the nonparametric Wilcoxon Mann-Whitney test was used to compare the means among the groups. These calculations were performed with the statistical package software SPSS for Windows (version 7.5.1). *P* values of .05 or less were considered statistically significant.

## RESULTS

The mean GSM and the mean degree of stenosis, with 95% confidence intervals, for symptomatic and asymptomatic plaques are illustrated in Table I. Figs 4 and 5 show the error bars for the GSM and the degree of stenosis in asymptomatic and symptomatic plaques. Plaques associated with symptoms were more hypoechoic (low GSM; *P* < .001) and more stenotic than plaques that were not associated with symptoms (*P* < .05)

Plaques associated with AF were more hypoechoic (*P* ≤ .003) and more stenotic (*P* ≤ .05) than plaques associated with TIA or stroke or with no symptoms. Plaques causing TIA and stroke have the same echodensity (*P* = .84) and the same degree of stenosis (*P* = .74). Table II shows the mean GSM and the mean degree of stenosis, with 95% confidence intervals, for the four groups of plaques. Figs 6 and 7 show the error bars for the GSM and the degree of stenosis in the four groups of plaques. Table III illustrates the between-group differences of the means.

## DISCUSSION

Currently, stroke-risk assessment in patients with carotid bifurcation disease is based on the degree of stenosis. Both the European Carotid Surgery Trial (ECST) study[1] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) study[2] concluded that, in symptomatic patients, carotid endarterectomy is beneficial, provided that the lesion is causing severe stenosis.

High-resolution ultrasound scanning provides in vivo information not only on the degree of stenosis, but also on the arterial wall changes, including the size and consistency of the atherosclerotic plaque. Different classifications have been proposed in the literature according to plaque consistency, resulting in considerable confusion. Plaques containing medium- or high-level echoes were classified as homogenous by Reilly et al[25] and correspond closely to Johnson's dense and calcified plaques,[3] to Gray-Weale's type 3
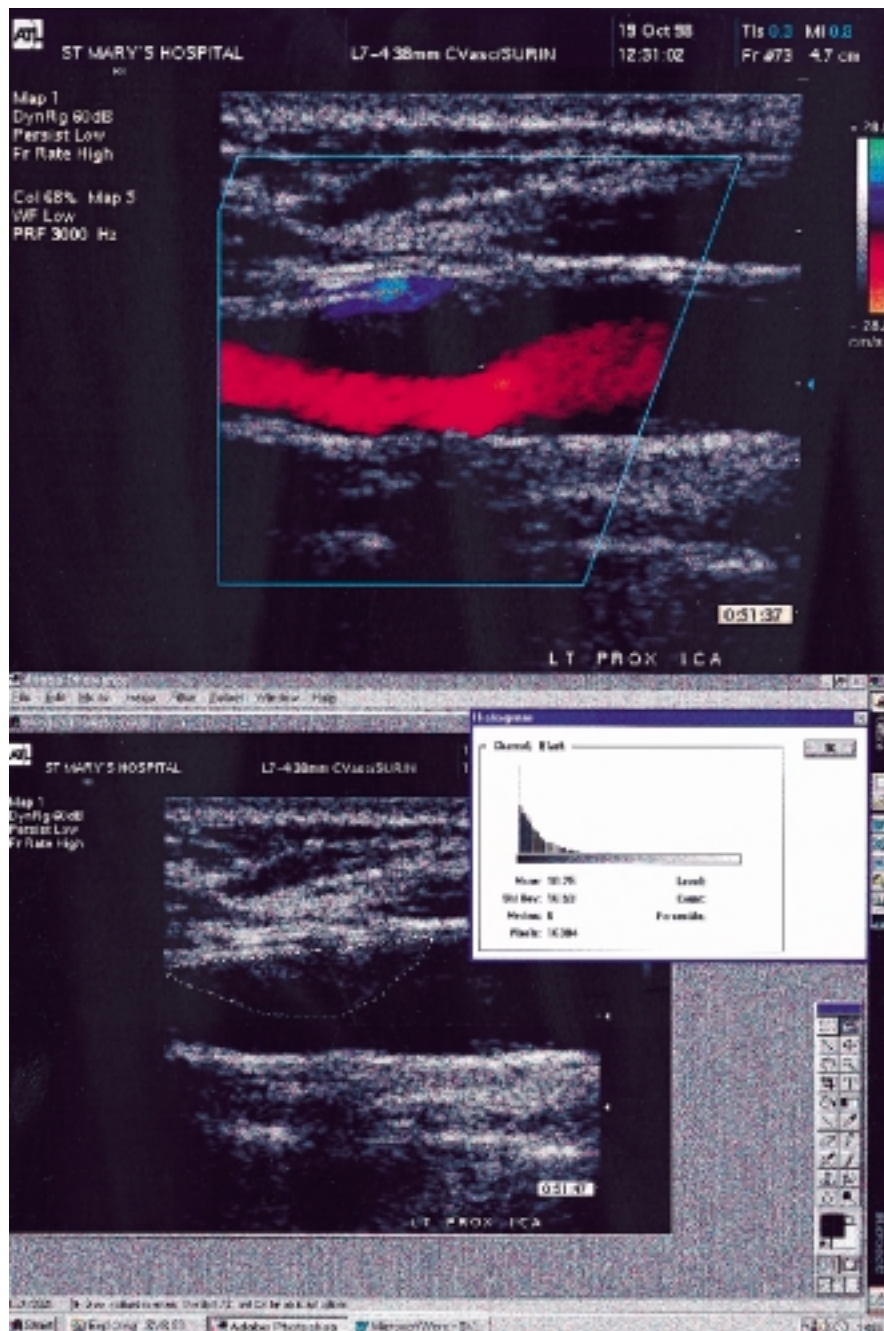
**Fig 2.** Hypoechoic plaque (gray scale median = 0) with the histogram of the gray tone frequency distribution of the pixels in the selected area (plaque) of the image. The colored image is used as a guide to outline the area of interest.

and 4 plaques,[26] and to Widder's type I and II plaques[27] (ie, echogenic or hyperechoic). A recent consensus on carotid plaque characterization has suggested that echodensity measurements should be used to reflect the overall brightness of the plaque, with the term "hyperechoic" referring to echogenic and the term "hypoechoic" referring to echolucent plaques.[28] The terms "homogenous" and "heterogenous" should be used for plaques of uniform or nonuniform consistency, respectively, thus expressing their ultrasonic texture (Fig 8). The reference structure to which plaque echodensity should be compared is
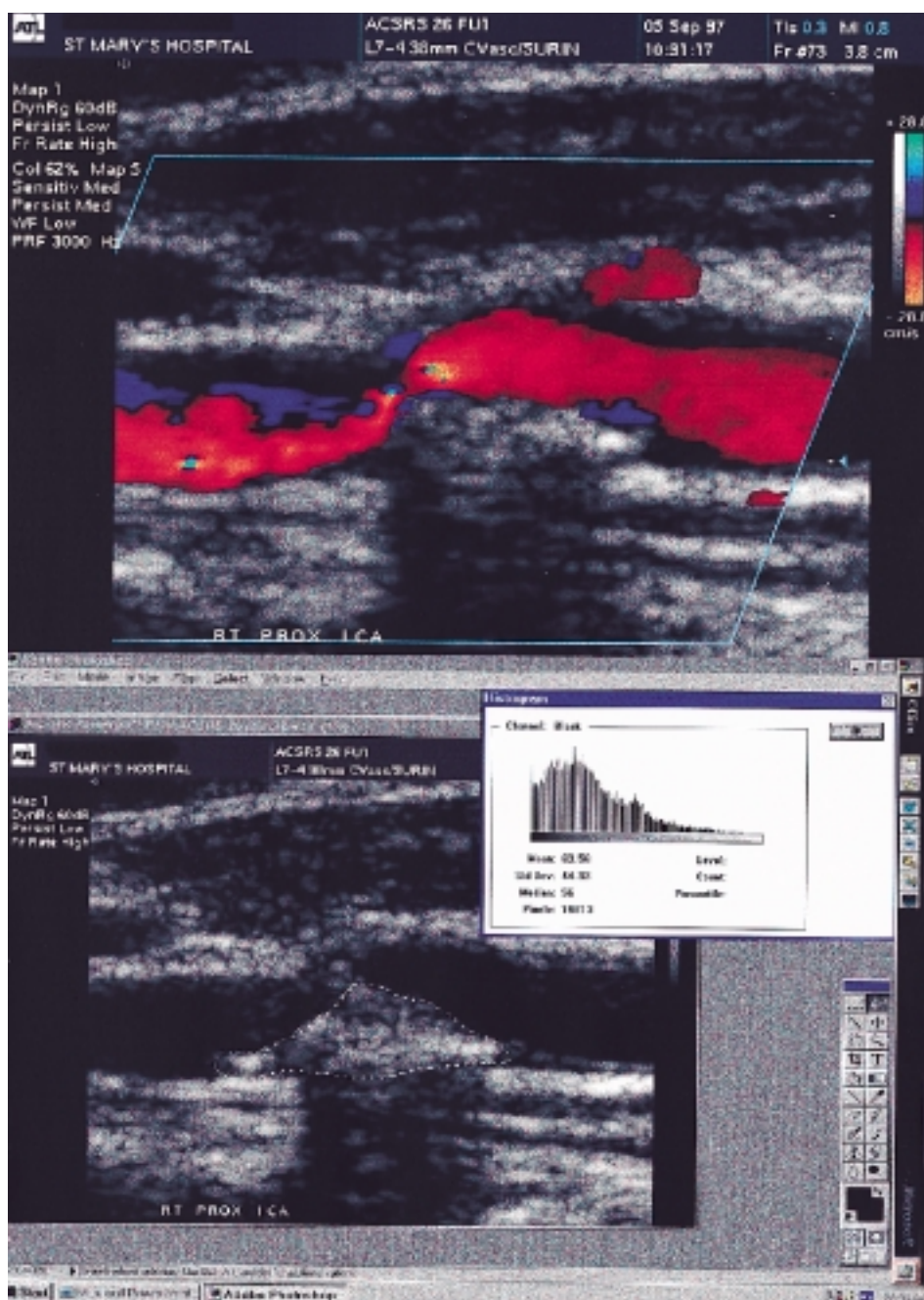
**Fig 3.** Hyperechoic plaque (gray scale median = 56) with the histogram of the gray tone frequency distribution of the pixels in the selected area (plaque) of the image.

blood for hypoechoic plaques, the sternomastoid muscle for isoechoic plaques, and the bone of the adjacent cervical vertebrae for hyperechoic plaques.

Computer-assisted plaque characterization with B-mode image normalization by means of digital image processing has been proposed by our group to be a reliable method for the objective and quantitative assessment of carotid plaque echomorphology.[24] To perform digital image processing with linear scaling, two reference points are necessary instead of one. The two reference points used in our method are blood and adventitia, which are always present and at the
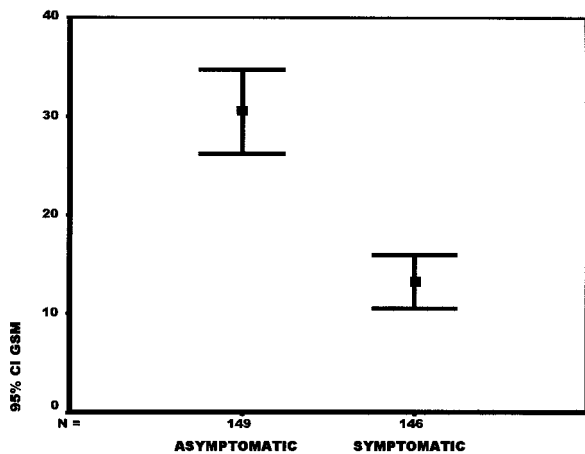
**Fig 4.** Error bars for the gray scale median in asymptomatic and symptomatic plaques.
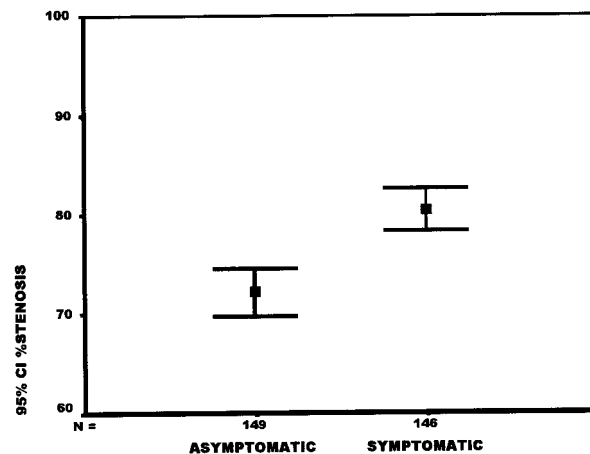


**Fig 5.** Error bars for the degree of stenosis in asymptomatic and symptomatic plaques.

**Table I.** The mean gray scale median and the mean degree of stenosis with 95% CI in plaques associated with hemispheric symptoms and plaques with no symptoms

| | GSM | | Stenosis | |
|---|---|---|---|---|
| | *Mean ± SD* | *95% CI* | *Mean ± SD* | *95% CI* |
| Hemispheric symptoms | 13.3 ± 16.6 | 10.6 to 16.0 | 80.5 ± 13.3 | 78.3 to 82.7 |
| No symptoms | 30.5 ± 26.2 | 26.2 to 34.7 | 72.2 ± 14.5 | 69.8 to 74.5 |
| *P* value* | | < .001 | | < .05 |

*Wilcoxon Mann-Whitney test.
*GSM,* Gray scale median.

**Table II.** The mean gray scale median and the mean degree of stenosis with 95% CI in plaques associated with amaurosis fugax, transient ischemic attack, stroke, and no symptoms

| | GSM | | Stenosis | |
|---|---|---|---|---|
| | *Mean ± SD* | *95% CI* | *Mean ± SD* | *95% CI* |
| AF | 7.4 ± 16.4 | 1.9 to 12.9 | 85.6 ± 10.6 | 82.0 to 89.2 |
| TIA | 14.9 ± 15.3 | 11.2 to 18.6 | 79.3 ± 12.9 | 76.1 to 82.4 |
| Stroke | 15.8 ± 18.0 | 10.2 to 21.3 | 78.1 ± 15.1 | 73.4 to 82.8 |
| No symptoms | 30.5 ± 26.2 | 26.2 to 34.7 | 72.2 ± 14.5 | 69.8 to 74.5 |

*GSM,* Gray scale median; *AF,* amaurosis fugax; *TIA,* transient ischemic attacks.

same depth as the carotid plaque. These are the only reference points used for every carotid plaque B-mode image, irrespective of whether the plaque is hypoechoic, isoechoic, or hyperechoic. Plaque characterization is expressed as a number by means of the GSM. As a result, variability caused by subjective classification of carotid plaques is avoided.

Reproducibility studies for the interobserver variability in normalizing B-mode carotid plaque images and measuring the GSM of the plaque revealed a mean GSM difference of 4.0 ± 0.8 and a coefficient of variation of 4.7%. Furthermore, the correlation coefficient for the GSM of plaques stored on a magneto-optical disk and on video was 0.99.[24]

In the study by Streifler et al,[15] the ipsilateral stroke-risk at 2 years in patients with high-grade carotid stenosis who presented with AF was found to be 16.6%. This is considerably lower than the risk for patients who presented with TIA, which was 43.5% at 2 years.
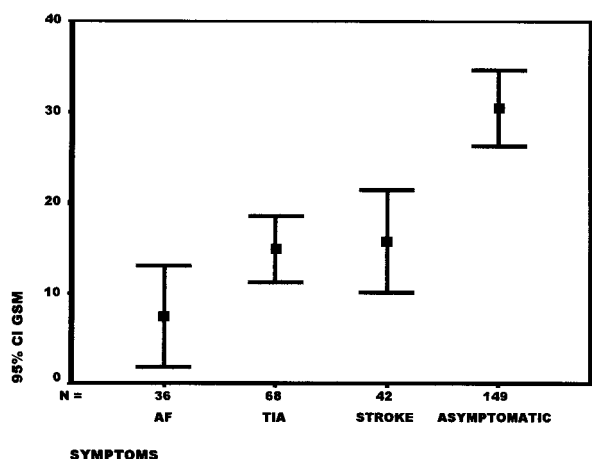
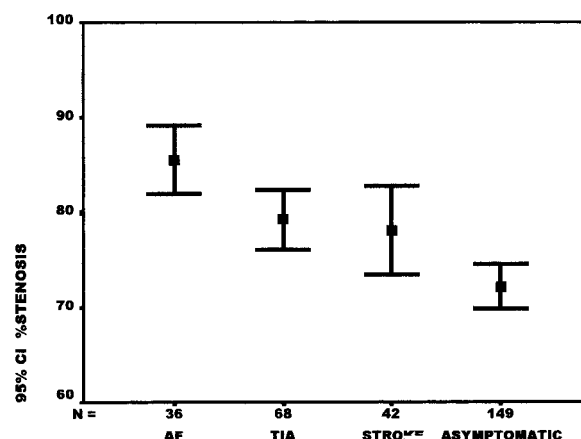**Fig 6.** Error bars for the gray scale median in the four groups of plaques.

**Table III.** Between-group differences of the means

|  | GSM (P value)* | Stenosis (P value)* |
|---|---|---|
| AF vs TIA | < .001 | .02 |
| AF vs stroke | .003 | .05 |
| AF vs no symptoms | < .001 | < .001 |
| TIA vs stroke | .84 | .74 |
| TIA vs no symptoms | < .001 | .001 |
| Stroke vs no symptoms | < .001 | .02 |

*Wilcoxon Mann-Whitney test.
*GSM,* Gray scale median; *AF,* amaurosis fugax; *TIA,* transient ischemic attack.



**Fig 7.** Error bars for the degree of stenosis in the four groups of plaques.
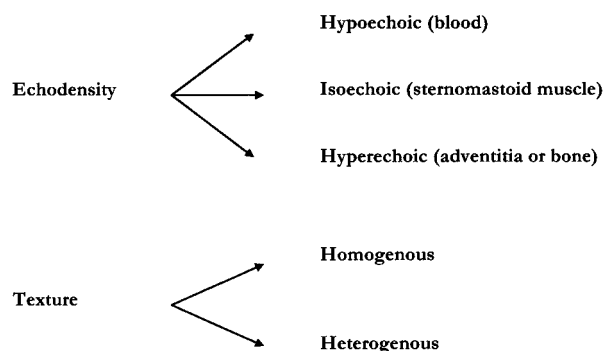


**Fig 8.** Classification of ultrasonic carotid plaque images, which distinguishes echodensity from texture.

Other studies have suggested that the stroke- and death-risk after carotid endarterectomy depend on the type of presenting symptom, with AF having a more favorable outcome.[29-31] In a recently published systematic review by Rothwell et al[16] regarding the risk factors for operative stroke and death from carotid endarterectomy, no overall difference was found between patients who had surgery for stroke and patients who had surgery for TIA. They concluded that the real dichotomy is not between stroke and TIA, but between retinal and cerebral ischemia.

Holdsworth et al,[32] in a cross-sectional study of individuals with 20% to 99% internal carotid artery stenosis, studied the association of carotid plaque echomorphology and the degree of stenosis with hemispheric symptoms. They found only AF to be associated with hypoechoic plaques. However, the degree of stenosis overall was more predictive of future events. It was apparent, however, that 23.5% of the plaques presenting with AF were associated with degrees of stenoses greater than 80%, whereas

the figures for plaques associated with TIA and stroke were 7.7% and 10.1%, respectively.

In our group of patients, the plaques associated with AF were causing very high-grade stenoses and were hypoechoic. It is likely that AF is a different manifestation of the embolic activity of the plaque, which interferes with the perfusion of the exquisitely sensitive retina, in contrast to the less sensitive cortical tissue. In addition, a tight carotid stenosis may be associated with increased turbulence and a predisposition to platelet aggregation in the poststenotic cul-de-sac.[33]

Our results confirm the findings that hypoechoic plaques are associated with a higher incidence of symptoms and furthermore show that plaques related to TIA or stroke are not as hypoechoic nor as stenotic as those related to AF. In addition, there is no significant difference in the degree of echodensity and stenosis

between them. It may be that these plaques are hypo-echoic but more heterogenous and, therefore, more rupture-prone, producing larger debris (plaque constituents or thrombi) that deprive larger areas of the brain of adequate perfusion than the smaller thrombi produced by the more stenotic and more homogenous hypoechoic plaques associated with AF.

Although the role of the biomechanical forces in the induction of plaque constituents fatigue is complicated and not well understood, the relationship between plaque composition and the location of peak stresses has been emphasized.[34-36] It is tempting to speculate that the proximity of the lipid-rich, hypoechoic areas of the plaque with the fibrotic and/or calcified, hyperechoic areas increases the peak stresses significantly, leading to plaque rupture with subsequent cerebral events. It has been suggested that very severe stenoses tend to have lower stresses on the fibrous cap, because the radius of the curvature of the lumen is small.[37] The less stenotic, hypoechoic but more heterogenous carotid plaques, consisting of a necrotic core and areas of fibrosis and/or calcification, may be more vulnerable to rupture than plaques only consisting of a large necrotic core and causing very severe stenosis.

To our knowledge, this is the first time that structural differences of carotid plaques detected by means of echodensity and degree of stenosis have been associated with different hemispheric symptoms. This may provide insight in the different pathophysiology of these symptoms. Future studies should aim at identifying the relationship between histologic features, rheologic features, mechanical stresses within the atherosclerotic plaque, and different symptomatology.

**REFERENCES**

1. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: Final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-87.
2. North American Symptomatic Carotid Endarterectomy Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998;339:1415-25.
3. Johnson JM, Kennelly MM, Decesare D, Morgan S, Sparrow A. Natural history of asymptomatic carotid plaque. Arch Surg 1985;120:1010-2.
4. Sterpetti AV, Schultz RD, Feldhaus RJ, Davenport KL, Richardson M, Farina C, et al. Ultrasonographic features of carotid plaque and the risk of subsequent neurologic deficits. Surgery 1988;8:558-62.
5. Langsfeld M, Gray-Weale AC, Lusby RJ. The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries. J Vasc Surg 1989;9:548-57.
6. Bock RW, Gray-Weale AC, Mock PA, Robinson DA, Irwig L, Lusby RJ. The natural history of asymptomatic carotid artery disease. J Vasc Surg 1993;17:160-9.
7. Geroulakos G, Ramaswami G, Nicolaides A, James K, Labropoulos N, Belcaro G, et al. Characterisation of symptomatic and asymptomatic carotid plaques using high-resolution real-time ultrasonography. Br J Surg 1993;80:1274-7.
8. Geroulakos G, Domjan J, Nicolaides A, Stevens J, Labropoulos N, Ramaswami G, et al. Ultrasonic carotid artery plaque structure and the risk of cerebral infarction on computed tomography. J Vasc Surg 1994;20:263-6.
9. El-Barghouty NM, Geroulakos G, Nicolaides A, Androulakis A, Bahal V. Computer-assisted carotid plaque characterisation. Eur J Vasc Surg 1995;9:389-93.
10. Polak JF, Shemanski L, O'Leary DH, Lefkowitz D, Price TR, Savage PJ, et al, for the Cardiovascular Health Study. Hypoechoic plaque at ultrasound of the carotid artery: An independent risk factor in adults aged 65 years or older. Radiology 1998;208:649-54.
11. Leen EJ, Feeley M. Colgan MP, O'Malley MK, Moore DJ, Hourihane DOB, et al. "Haemorrhagic" carotid plaque does not contain haemorrhage. Eur J Vasc Surg 1990;4:123-8.
12. Feeley TM, Leen EJ, Colgan MP, Moore DJ, Hourihane DOB, Shanik GD. Histologic characteristics of carotid artery plaque. J Vasc Surg 1991;13:719-24.
13. Grønholdt MLM, Wiebe BM, Laursen H, Nielsen TG, Schroeder TV, Sillesen H. Lipid-rich carotid artery plaques may appear echolucent on ultrasound B-mode images and may be associated with intraplaque haemorrhage. Eur J Vasc Endovasc Surg 1997;14:439-45.
14. Grønholdt MLM, Nordestgaard BG, Wiebe BM, Wilhjelm JE, Sillesen H. Echo-lucency of computerized ultrasound images of carotid atherosclerotic plaques are associated with increased levels of triglyceride-rich lipoproteins as well as increased plaque lipid content. Circulation 1998;97:34-40.
15. Streifler JY, Eliaziw M, Benavente OR, Harbinson JW, Hatchinski VC, Barnett HJM, et al for the North American Symptomatic Carotid Endarterectomy Trial. The risk of stroke in patients with first-ever retinal versus hemispheric transient ischemic attacks and high-grade carotid stenosis. Arch Neurol 1995;52:246-9.
16. Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: Systematic review. BMJ 1997;315:1571-7.
17. Moneta GL, Edwards JM, Chitwood RW, Taylor LM, Lee RW, Cummings CA, et al. Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 90% internal carotid artery stenosis with duplex scanning. J Vasc Surg 1993;17:152-9.
18. Moneta GL, Edwards JM, Papanicolaou G, Hatsukami T, Taylor LM Jr, Strandness ED Jr, et al. Screening for asymptomatic internal carotid artery stenosis: Duplex criteria for discriminating 60% to 99% stenosis. J Vasc Surg 1995;21:989-94.
19. Breslau PJ. Ultrasonic duplex scanning in the evaluation of carotid artery disease [thesis]. Maastricht, Holland; 1981.
20. Nicolaides AN, Shifrin EG, Bradbury A, Dhanjil S, Griffin M,

Belcaro G, et al. Angiographic and duplex grading of internal carotid stenosis: Can we overcome the confusion? J Endovasc Surg 1996;3:158-65.

21. Dhanjil S, Jameel M, Nicolaides AN, Belcaro G, Williams M, Griffin M, et al. Ratio of peak systolic velocity of internal carotid to end diastolic velocity of common carotid: New duplex criteria for grading internal carotid stenosis. J Vasc Technol 1997;21:237-40.

22. Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987;15:635-744.

23. deBray JM, Glatt B. Quantification of atheromatous stenosis in the extracranial internal carotid artery. Cerebrovasc Dis 1995;5:414-26.

24. El-Atrozy T, Nicolaides A, Tegos T, Zarka AZ, Griffin M, Sabetai M. The effect of B-mode image standardisation on the echodensity of symptomatic and asymptomatic carotid bifurcation plaques. Int Angiol 1998;17:179-86.

25. Reilly LM, Lusby RJ, Hughes L, Ferrell LD, Stoney RJ, Ehrenfeld WK. Carotid plaque histology using real-time ultrasonography: Clinical and therapeutic implications. Am J Surg 1983;146:188-93.

26. Gray-Weale AC, Graham JC, Burnett JR, Byrne K, Lusby RJ. Carotid artery atheroma: Comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. J Cardiovasc Surg 1988;29:676-81.

27. Widder B, Paulat K, Hachpacher J, Hamann H, Hutschenreiter S, Kreutzer C, et al. Morphological characterisation of carotid artery stenoses by ultrasound duplex scanning. Ultrasound Med Biol 1990;16:349-54.

28. deBray JM, Baud JM, Dauzat M for the Consensus Conference. Consensus concerning the morphology and the risk of carotid plaques. Cerebrovasc Dis 1997;7:289-96.

29. Troeng T, Bergqvist D, Elfstrom J, Hedberg B, Ljungstrom KG, Ortenwall P, et al. Outcome assessment in vascular surgery—The Swedish experience. J Vasc Surg 1995;22:810-1.

30. Golledge J, Cuming R, Beattie DK, Davies AH, Greenhalgh RM. Influence of patient-related variables on the outcome of carotid endarterectomy. J Vasc Surg 1996;24:120-6.

31. Blohme L, Sandstrom V, Hellstrom G, Swedenborg J, Takolander R. Complications in carotid endarterectomy are predicted by qualifying symptoms and preoperative CT findings. Eur J Vasc Endovasc Surg 1999;17:213-8.

32. Holdsworth RJ, McCollum PT, Bryce JS, Harrison DK. Symptoms, stenosis and carotid plaque morphology. Is plaque morphology relevant? Eur J Vasc Endovasc Surg 1995;9:80-5.

33. The Amaurosis Fugax Study Group. Current management of amaurosis fugax. Stroke 1990;21:201-8.

34. Richardson PD, Davies MJ, Born GVR. Influence of plaque configuration and stress distribution and fissuring of coronary atherosclerotic plaque. Lancet 1989;2:941-4.

35. Ku DN, McCord BN. Cyclic stress causes rupture of the atherosclerotic plaque cap. Circulation 1993;88(Suppl):1362.

36. Glagov S, Bassiouny HS, Sakaguchi CA, Goudet CA, Vito RP. Mechanical determinants of plaque modeling, remodeling and disruption. Atherosclerosis 1997;131Suppl:S13-S14.

37. Loree HM, Kamm RD, Stringfellow RG, Lee RT. Effect of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels. Circ Res 1992;71:850-8.

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## DISCUSSION

**Dr Hisham S. Bassiouny** (Chicago, Ill). I would like to congratulate Mr Nicolaides and his group for their efforts in attempting to elucidate the clinical relevance of carotid bifurcation plaque ultrasound scanning echodensity.

In this report, they propose that, by using objective and quantitative measures of plaque lucency in high-grade stenoses, it is possible to discriminate between symptomatic and asymptomatic plaques and between symptomatic plaques associated with either ipsilateral, ocular, or hemispheric events. They have concluded that symptomatic plaques are more echolucent than asymptomatic plaques and that in symptomatic plaques associated with amaurosis fugax, these plaques were more echolucent than plaques associated with hemispheric transient ischemic attack or stroke.

On review of the manuscript, two key observations are evident. First, the technology used in the quantitative assessment of carotid plaque lucency is plausible and uses user-friendly software; and second, plaque echolucency is proportionate to carotid bifurcation burden. If it is assumed that the ultrasound echolucency represents necrotic, hemorrhagic, or thrombotic regions in the plaque, then such structural features appear to be proportionate to the severity of carotid stenoses, rather than the symptomatic nature of the plaque.

In this study, the degree of carotid stenoses was different between the asymptomatic and the various symptomatic patient subgroups. However, this important independent variable was uncontrolled for by logistic regression analysis to isolate the independent contribution of plaque echolucency in clinical events. Herein lies one of the potential pitfalls of the study.

We have previously reported our findings regarding the histopathologic features of carotid endarterectomy specimens. We found that similar degrees of carotid stenoses share similar plaque, structural, and chemical components, regardless of symptoms. Nonetheless, the spatial distribution of plaque echolucent components in relationship to the abluminal fibrous cap emerged as a critical histopathologic feature in discriminating between symptomatic and asymptomatic plaques. For example, in a given 80% stenosis, a plaque with a large necrotic core that resides near the adventitia is more stable and less likely to be symptomatic than a plaque with a similar degree of stenosis in which the necrotic core is proximate to the abluminal or otherwise eroding fibrous cap. These findings would suggest that the location of echolucency in relation to the lumen, rather than its size, is a critical feature of plaque instability and symptoms.

I therefore have four questions.

First, did you compare the degree of echolucency in symptomatic subgroups of patients with plaques of similar degrees of stenosis?

Second, if your results are indeed reproducible, how do you explain the greater echolucency of plaques with amaurosis fugax in light of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) results, which indicate a reduced stroke-risk for patients with amaurosis fugax in contrast to patients with transient ischemic attack or mild stroke? What was the interval between the carotid ultrasound scanning evaluation and the patient's initial ocular or hemispheric event? A plaque that is symptomatic today may heal and remodel and become asymptomatic in due time.

Next, how did you calculate such precise degrees of stenoses? I understand from the manuscript that only the internal carotid artery/common carotid artery ratio was used to grade the stenoses. Were there any angiographic correlates?

My final question relates to the technique of the image acquisition. Only one single sagittal image of the plaque was used for measuring echolucency. What criteria did you use to select the representative ultrasound scanning section? Perhaps a more reliable quantitative technique would have involved an axial cross-sectional analysis. More important, did you correlate your findings with any histopathologic analyses of plaques removed at endarterectomy?

I enjoyed reading the manuscript, and I thank the Society for the opportunity to discuss it.

**Professor Andrew N. Nicolaides.** Thank you for your comments and your questions.

Let's start with the first question, about the comparison of the degree of echolucency in symptomatic subgroups of patients with plaques of similar degrees of stenosis. Actually, we plotted the degree of stenosis on the vertical axis against the gray scale median, that is, echodensity, along the horizontal axis, and then the results were in front of us. There were two separate clusters, one for the amaurosis fugax and one for the transient ischemic attack and stroke, with some overlap. If you take this overlap and take plaques of different symptoms with the same degree of stenosis, it is obvious that those with amaurosis fugax had a lower gray scale median; they were darker, although the degree of stenosis was the same. So the answer is yes; we did compare the degree of echolucency.

Answering the second question is more difficult. First, I would like to say that the tendency of patients with amaurosis fugax to have darker plaques, type 1 and type 2, and to have tight stenosis greater than 80% is not an original finding of ours. It was initially reported by Holdsworth in a paper published in 1995 in the *European Journal of Vascular Surgery*. But it was interesting that we found the same tendency not just by looking at the plaques, but by making computer measurements.

You have heard the hypothesis at the end of Dr Sabetai's presentation. We had to think very, very hard to produce this hypothesis, which is: If you have an echolucent plaque that is full of cholesterol, the stresses in the plaque with each heartbeat are the same, and it tends to accumulate more and more cholesterol without rupturing, until it gets very, very tight, to 90% stenosis or more. You

have a fine jet going through it. You have turbulence and platelets beyond it, aggregates form, and then they give amaurosis fugax.

On the other hand, if you have a plaque that is slightly brighter, is heterogenous, and has areas that are fibrotic and areas that are not fibrotic, the hypothesis says that the stresses in the plaque are such that, with each heartbeat, they make it to rupture and, therefore, it produces transient ischemic attack and stroke before it gets to 90% to 95% stenosis. It is very hard to prove. To prove this, we have to use the new algorithms and the new computer programs that study the deformation of plaques, when you videotape them, and use computer techniques to study them with each heartbeat. I think that's what will come in the next few years.

How did we calculate the precise degrees of stenosis? We used two ratios. We used the ratio of the peak systolic velocity of the internal carotid artery divided by the peak systolic velocity of the common carotid artery, as described by Dr Moneta, and this gave us the two cutoff points, 60% and 70%.

We also used an additional ratio, the ratio of the peak systolic velocity of the internal carotid divided by the end diastolic velocity of the common carotid, initially described by Breslau in the early 1980s, when he was working with Dr Strandness. Since then, this ratio has been validated by us with angiography and was published in the *Journal of Endovascular Surgery* in 1996. This ratio gives three very good cutoff points, at 70%, 80%, and 90% stenosis, with a plus or minus 7% error rate. This is shown against angiography. You are quite right to pick up this point. There is an error in the manuscript, and we have added the extra line.

Your fourth question was about the plane used for measuring echolucency and how we quantified it. We conducted a reproducibility study, in which we took images anteriorly, laterally, and posteriorly by the sternomastoid muscle, and we found that an anterior image, a longitudinal section on duplex, and the lateral image were similar. The gray scale median of the plaque did not change. But when we took a posterior view by the sternomastoid, the echodensity did change; the plaques were brighter. Therefore, we suggest you stick to the anterior anterolateral view, and it does not matter if you move your probe an angle of 30 degrees, the echodensity is not going to change.

Finally, we have not correlated our findings with histopathologic analysis yet; we are doing this now. Thank you.

**Dr James M. Estes** (Highlands, NC). I also congratulate you on presenting a very innovative and scientific analysis of ultrasound plaque morphology. But as Dr Bassiouny pointed out, you are still really looking at gross morphologic features of the plaque. In light of your experience in this area, can you comment on the feasibility of studying specific plaque features, such as the fibrous cap thickness, by means of current imaging and modalities?

**Professor Nicolaides.** Thank you. That is a very good question. If you asked me that question 3 years ago, I would have said no. But having seen the latest equipment that is available, I think I am beginning to say yes. And the best example in support of this is the work that has come from Professor Fernandez's department in Lisbon, in which they looked at heterogenous plaques and found that if a black area was very close to the lumen, it was associated with an increase event rate in comparison with the asymptomatic plaques. Also, if the fibrous cap could not be seen, if there was an acoustic hole, it suggested that there was a thin fibrous cap, and those plaques tended to be symptomatic rather than asymptomatic. But I think we have to wait and see what will come from this work.

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