Ultrasonic plaque character and outcome after lower limb angioplasty

Ganesh Ramaswami, MD, PhD, Thomas Tegos, MD, Andrew N. Nicolaides, MD, FRCS, Surinder Dhanjil, MS, RVT, Maura Griffin, MS, Aghiad Al-Kutoubi, MD, FRCR, Gianni Belcaro, MD, John Lewis, MD, FRCS, Robert Wilkins, MD, FRCR, and **Michael J. Davies, MD, FRCS,** *London, United Kingdom*

Purpose: **The value of ultrasonic plaque characteristics in identifying patients at "high-risk" of restenosis after percutaneous transluminal angioplasty (PTA) was studied.**
Methods: **Thirty-one arterial stenoses (6 common iliac, 2 external iliac, 1 profunda femoris, 21 superficial femoral, and 1 popliteal) in 17 patients who underwent angioplasty were studied by means of duplex scanning. With a computer-based program, B-mode images were digitized and normalized using 2 reference points, blood and adventitia. A grey level of 0 to 5 was allocated for the lumen (blood) and 180 to 190 for the adventitia on a linear gray scale of 0 to 255 (0 = absolutely black; 255 = absolutely white), and the overall plaque gray-scale median (GSM) of the pixels of the plaque was used as a measure of plaque echodensity. After PTA, follow-up of stenoses was done on day 1, weekly for 8 weeks, at 3 months, 6 months, and 1 year. The total plaque thickness (sum of anterior and posterior components), minimal luminal diameter (MLD), and peak systolic velocity ratio (PSVR) were measured for all stenoses. An increase of more than 2 in the PSVR was the duplex criterion used to signify restenosis.**
Results: **The GSM of the stenoses before angioplasty ranged from 6 to 71 (mean, 31.3 ± 17.9); 17 stenoses had a GSM less than 25 (mean, 18.7 ± 5.3), and 14 had a GSM more than 25 (mean, 46.4 ± 15.8). When the GSM was less than 25, the absolute reduction in plaque thickness on day 1 post-PTA was 3.3 ± 1.8 mm, in contrast to 1.8 ± 1.6 mm when GSM was more than 25 ($P < .03$). The restenosis rate (PSVR more than 2) was 41% at 6 months and remained unchanged at 1 year. When the GSM was less than 25, restenosis occurred in 11% of lesions, in comparison with 78% when the GSM was more than 25 ($P < .001$).**
Conclusion: **Plaque echodensity can be used to evaluate stenoses before PTA, to predict initial success and identify a subgroup that has a high prevalence of restenosis. The identification of a group at "high-risk" of restenosis can improve the selection of patients for the procedure and also be used in prospective studies on the prevention of restenosis.**
(J Vasc Surg 1999;29:110-21.)

Ultrasonic carotid plaque characteristics[1,2] have revealed that echolucent plaques are more frequently associated with neurologic events than echogenic ones.[3,4] Recent publications[5,6] have suggested that computer-based assessment of plaque characteristics may be a more objective, operator-independent method for the assessment of plaque echodensity and the identification of high-risk carotid lesions.

The long-term efficacy of lower limb balloon angioplasty is limited by restenosis at the site of angioplasty. Angioplasty works by the mechanism of disruption and compaction of plaque, with a resultant increase in minimal luminal diameter. Our group has shown that duplex scanning can be effectively used to study the restenotic process after angioplasty in iliac and femoropopliteal arteries by means of frequent measurement of plaque thickness, minimal luminal diameter (MLD), and peak systolic velocity ratio (PSVR) at the site of angioplasty,[7] and

From the Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit, Imperial College School of Medicine at St. Mary's, the Department of Radiology, St. Mary's Hospital, and the Departments of Surgery and Radiology, Northwick Park Hospital.
Presented at the Fifty-second Annual Meeting of The Society for Vascular Surgery, San Diego, Calif, June 9–10, 1998.
Reprint requests: Ganesh Ramaswami, Department of Surgery, 15th Floor, 5 East 98 St, Box 1259, Mount Sinai Hospital, New York, NY 10029.

0741-5214/99/$8.00 + 0 **24/6/93818**

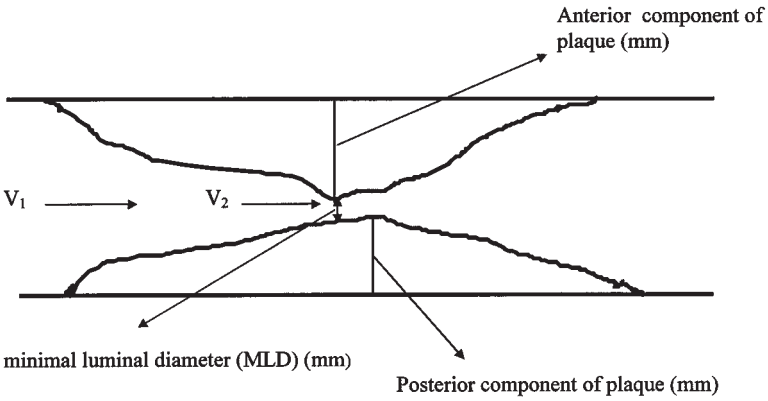

Fig 1. Measurements made for each stenosis: **A,** thickness of anterior component of plaque (mm); **B,** thickness of posterior component of plaque (mm); **C,** minimal luminal diameter (MLD; mm); **D,** V_2, velocity at site of stenosis (cm/s); V_1, velocity proximal to stenosis (cm/sec); peak systolic velocity ratio (PSVR) = V_2/V_1. An increase in the PSVR of more than 2, in the follow-up period after angioplasty signified restenosis.

this methodology has been described. The hypothesis tested by the work presented in this paper was that echolucent plaques with their higher content of cholesterol would be more compressible than echogenic fibrous plaques; therefore, the immediate and long-term outcome of angioplasty in these lesions would be different. The aim of this study was to determine (1) the relationship between ultrasonic plaque morphology and immediate outcome after angioplasty for (a) increase in MLD, (b) fall in PSVR, and (c) decrease in plaque thickness; and (2) the relationship between plaque morphology and long-term outcome for (a) plaque "growth" and (b) restenosis.

MATERIAL AND METHODS

Thirty-one stenoses in 17 patients (mean age, 63 years; 13 women/4 men) were included in the study. Informed consent to participate in the study was obtained from all patients, and the study was approved by the institutional review board. All lesions had more than 70% stenosis and were less than 5 cm long. The lesions were distributed in the common iliac (6), external iliac (2), profunda (1), superficial femoral (21), and popliteal (1) arteries. All scans were performed on the Hewlett-Packard Sonos 2000 color flow duplex scanner (Andover, Mass) with the same set of controls (transmit power, gain, pre- and post-processing curves, compress and regress) for all iliac examinations, and a different fixed preset was used for all femoropopliteal scans. All iliac scans were done at a depth of 4 to 8 cm, and femoropopliteal scans were done at a depth of 4 to 6 cm with a 4.5/3.5 MHz linear array transducer. Patients undergoing iliac scans fasted overnight to reduce bowel gas and were examined in the morning. All arteries were localized initially on transverse imaging and then examined in the longitudinal mode with the position of the transducer adjusted to obtain the maximum thickness of the anterior and posterior components of the plaque at the site of stenosis. Images obtained in B-mode and color were stored on a magneto-optical disk for future retrieval and analysis. Also, the site of stenosis in relation to landmarks was noted to enable easy localization for future examinations; the common femoral artery bifurcation and adductor tubercle were used for superficial femoral artery stenoses, and the anterior superior iliac spine, symphysis pubis, and umbilicus were used for iliac examinations. The presence of collaterals was also noted. Changes in plaque thickness in the anterior and posterior components, MLD, and PSVR at the site of angioplasty were measured by means of ultrasound, as shown in Fig. 1. For plaque measurement, the thickest portion of the plaque was measured, from the luminal surface to the adventitia. For the MLD, the narrowest portion of the lumen was measured. To avoid the pitfall of under or over measuring, both color and B-mode images were examined, because color helped to outline echolucent plaques. All measurements were performed with the help of on-screen calipers. For the measurement of PSVR, V2 and V1 were obtained from an average of 5 separate arterial waveforms. The results of interobserver variability studies for the measurement of plaque thickness, MLD, and PSVR have been report-

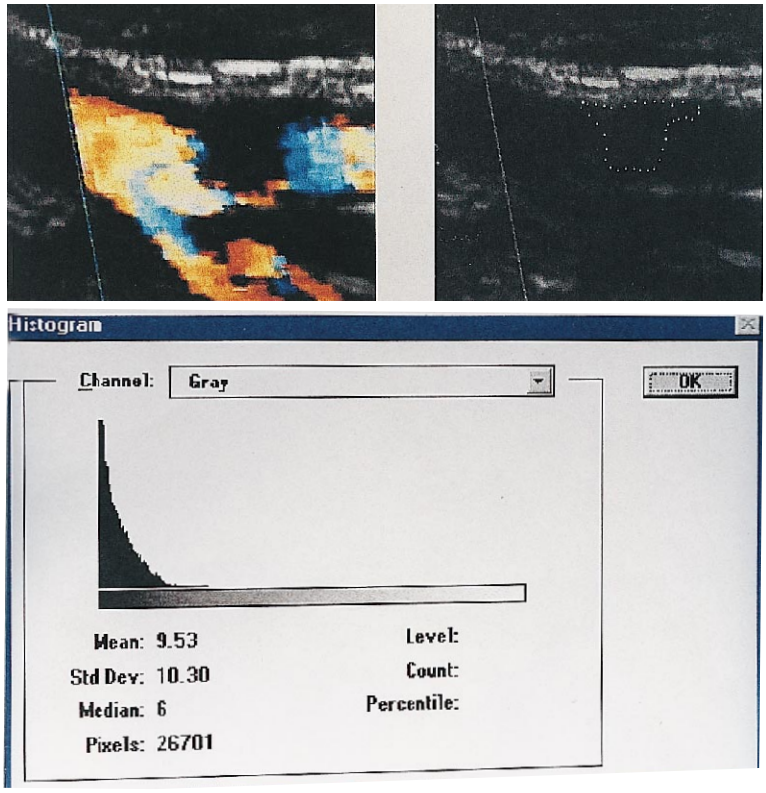

Fig 2. Gray-scale median (GSM) of a stenosis in the superficial femoral artery. The plaque was echolucent and had a GSM of 6.

ed by our group previously.[7] The correlation coefficient, mean absolute difference, and 95% limits of agreement were r = 0.90, 0.06 ± 0.26, –0.46 to 0.58 mm for plaque thickness; r = 0.91, –0.03 ± 0.46 mm, –0.49 to 0.43 mm for MLD; and r = 0.93, 0.04 ± 0.31, –0.27 to 0.35 for PSVR.

A baseline scan was performed either on the morning of or 1 day before angioplasty, and follow-up was done on day 1, weekly for the first eight weeks, week 12, week 24, and week 52 (1 year). An increase of more than 2 in the PSVR in the postangioplasty period was the criterion used to signify restenosis.

Assessment of plaque characteristics. The assessment of plaque characteristics was performed on baseline scans of all stenoses that were subjected to angioplasty with a computer-based program. For the purpose of computer-based assessment of plaque character, all digitized images were transferred from the magneto-optical disc to a Dell PC (120 MHz Pentium processor, 32 MB RAM; Dell Computer, Bracknell, UK). By means of a computer program (Adobe Photoshop, Adobe Systems, Mountain View, Calif), all B-mode images were normalized using 2 reference points, blood and adventitia. The darkest part of the lumen (blood) was assigned a gray level between 0 and 5, and the brightest portion of the adventitia was given a level between 180 and 190 on a linear scale of 0 to 255 (0 = absolutely dark; 255 = absolutely white). However, the outline of echolucent plaques may not be easily defined on B-mode imaging. Therefore, in instances in which plaques were echolucent, the color image was used to help the operator define the outline of the plaque. The plaque on the B-mode black-and-white image was then outlined with a computer mouse. The gray-scale median (GSM) of the pixels of the plaque was obtained and used as a measure of plaque echodensity. Figs. 2 and 3 illustrate the pixel histogram. The number of pixels is on the Y-axis, and the gray scale is on the X-axis. The GSM in Fig. 2 is 6, indicating an echolucent plaque; in contrast, the GSM in Fig. 3 is 35, indicating an echogenic plaque. The spectral broadening reflects the extent of homogeneity or heterogeneity. When a stenosis had both an anterior and posterior component, an average of the 2 medians was taken. All stenoses undergoing angioplasty had the GSM of plaques assessed before the procedure.

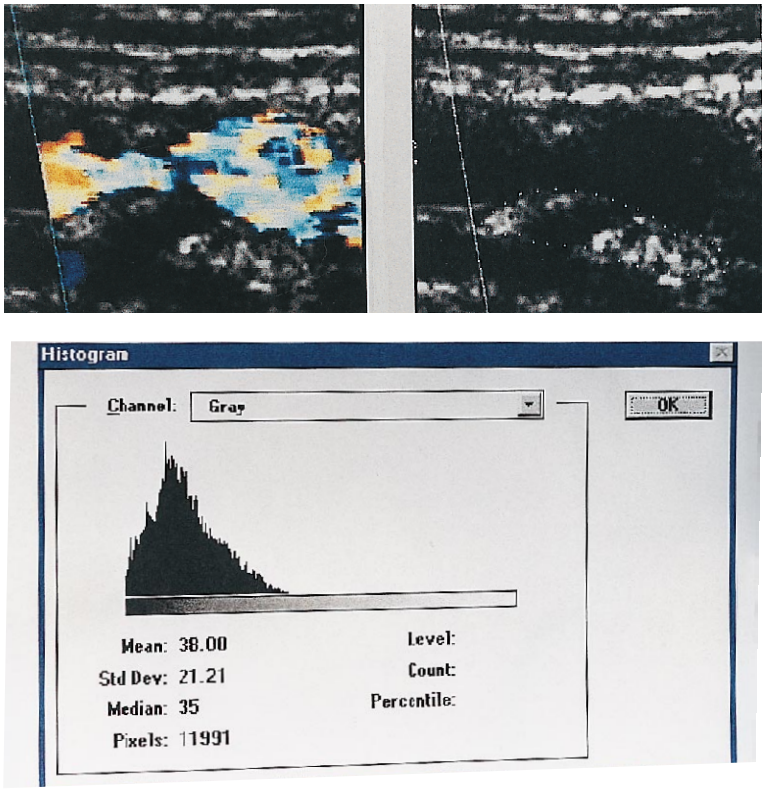

Fig 3. Gray-scale median (GSM) of a stenosis in the superficial femoral artery. The plaque was echogenic and had a GSM of 35.

Reproducibility of plaque gray-scale median. The reproducibility of GSM measurements was assessed by conducting an interobserver study between 2 of the authors (G.R. and T.T.); each observer independently standardized the images from the magneto-optical disc and obtained the mean gray scale of the plaque. The GSM of plaques from 30 stenoses were measured, and the results were compared. The results were analyzed for (1) between observer variability (coefficient of correlation [r]) and (b) 95% limits of agreement: the mean ± (2 SD) of the absolute difference in measurement between 2 observers.

Relationship between plaque gray-scale median and outcome after angioplasty. The relationship between plaque GSM and immediate outcome after angioplasty with regard to the total plaque thickness, minimal luminal diameter, and peak systolic velocity ratio was determined (Fig. 1). Also, the relationship between plaque GSM and restenosis for increase in PSVR of more than 2.0 and the absolute plaque "growth" in the postangioplasty period were studied. The following equations were used to calculate the reduction in plaque thickness immediately after angioplasty, increase in MLD, percent decrease in PSVR, and absolute plaque "growth" after angioplasty.

Reduction in plaque thickness immediately after angioplasty

Total plaque thickness preangioplasty (mm) = sum of anterior + posterior plaque (A)

Total plaque thickness on day 1 postangioplasty (mm) = sum of anterior + posterior plaque (B)

Absolute reduction in plaque thickness = A – B (mm).....(1).

Increase in minimal luminal diameter (MLD) after angioplasty

MLD (mm) preangioplasty = C

MLD (mm) postangioplasty = D

Absolute increase in MLD after angioplasty = D – C (mm).....(2)

Reduction in peak systolic velocity ratio (PSVR) after angioplasty

PSVR (preangioplasty) = E

PSVR (postangioplasty) = F

% decrease in PSVR = 100 – ([F/E] × 100).....(3)

Absolute plaque "growth" after angioplasty

Plaque thickness on day 1 (mm) = B

Plaque thickness at final visit or at time of restenosis (mm) = G

Absolute plaque "growth" (mm) = G – B.....(4)

RESULTS

The results of the interobserver variability for the measurement of plaque GSM of 30 stenoses showed a coefficient of correlation (r) of 0.93, and the 95% limit of agreement was –4.1 to 5.9.

Relationship between plaque GSM and immediate outcome after angioplasty. Fig. 4 is an example of an echolucent plaque in the superficial femoral artery with a GSM of 6. The anterior plaque was 4.31 mm, the MLD 1.14 mm, and the PSVR 2.85. Fig. 5 shows the same plaque on day 1 after angioplasty; the anterior plaque reduced in thickness to 1.32 mm (the absolute reduction in plaque thickness was 2.99 mm), the MLD increased to 5.02 mm (the absolute increase was 3.88 mm), and the PSVR decreased to 1.03 (the percent decrease was 64%). Angioplasty achieved its effect by means of compression of the echolucent plaque. Fig. 6 is an example of a fibrous plaque in the superficial femoral artery with a GSM of 35. The posterior plaque measured 3.96 mm, the MLD 2.11 mm, and the PSVR 2.46. Fig. 7 shows the same plaque on day 1 after angioplasty; the posterior plaque thickness was reduced to 3.91 mm (the absolute decrease in plaque thickness was 0.05 mm), the MLD increased to 3.69 mm (the absolute increase was 1.58 mm), and the PSVR decreased to 1.77 (the percent decrease was 28%). Angioplasty achieved its effect by means of dilatation of the arterial wall with minimal plaque compression.

The plaque GSM of the 31 stenoses subjected to angioplasty ranged from 6 to 71 (mean, 31.3 ± 17.9) (from echolucent to very echogenic [fibrous] plaques). For the purpose of analysis of the results, an arbitrary cutoff point of 25 in the GSM was taken to see if separation of the stenoses for outcome could be seen. Based on this, 2 groups were available for comparison of the results of angioplasty: group A, with a GSM less than 25, consisting of 17 stenoses (mean, 18.7 ± 5.3) and group B, with GSM greater than 25, consisting of 14 stenoses (mean 46.4 ± 15.8).

Table I. The relationship between plaque grey-scale median (GSM) and reduction in plaque thickness on day 1 after angioplasty

	Group A (GSM < 25)	*Group B (GSM > 25)*	*P value (t test)*
Plaque thickness (mm) (preangioplasty) (A)	5.6 ± 2.2	5.2 ± 2.2	NS
Plaque thickness (mm) (day 1 postangioplasty) (B)	2.2 ± 1.7	3.3 ± 0.9	NS
Absolute decrease in plaque thickness (mm) (A – B)	3.3 ± 1.8	1.8 ± 1.6	<.03

NS, not significant.

Table II. The relationship between plaque grey-scale median (GSM) and restenosis (peak systolic velocity ratio [PSVR] more than 2.0) ($P < .001$ with Yates correction)

	No stenosis (PSVR < 2.0)	*Stenosis (PSVR > 2.0)*	*Total*
Plaque GSM < 25	15	2 (11.8%)	17
Plaque GSM > 25	3	11 (78.8%)	14
Total	18	13	31

Table I shows the relationship between GSM and plaque thickness (mm), before and on day 1 after angioplasty. When the GSM was less than 25, the absolute reduction in plaque thickness (mm) on day 1 was significantly greater than when the GSM was greater than 25 ($P < .03$). There was no relationship between GSM and increase in MLD and percentage decrease in PSVR at the site of angioplasty.

Relationship between plaque gray-scale median and restenosis. The relationship between plaque GSM and restenosis based on the increase in PSVR of more than 2.0 is shown in Table II. When plaque GSM was less than 25, the incidence of restenosis was 12%, in comparison with a restenosis rate of 78% when the GSM was greater than 25 ($P < .001$, with Yates correction). The relationship between plaque GSM and PSVR is shown in Fig. 8 (r = 0.66).

The overall incidence of restenosis was 41% (13 of 31) at 24 weeks (6 months); there were no lesions that restenosed between weeks 24 and 52 (1 year). Two lesions with a GSM less than 25 restenosed at weeks 16 and 24. Of the lesions with a GSM greater than 25 that restenosed, 6 recurred before week 8 (55%), 3 before week 12 (28%), and 2 before week 24 (18%). A

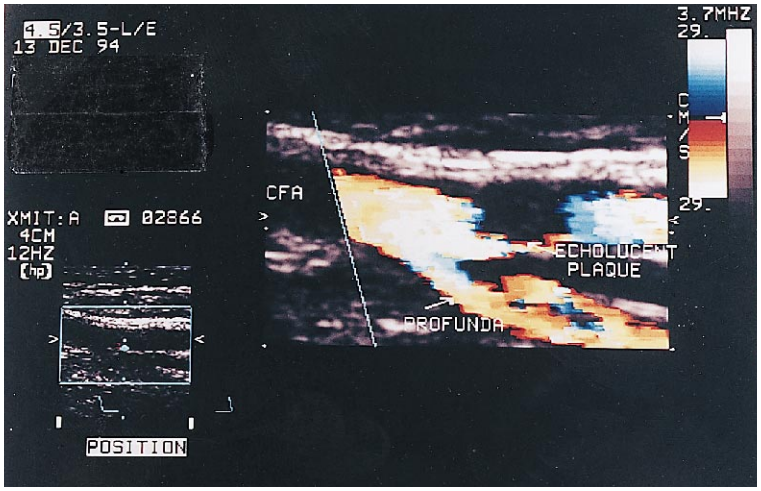

Fig 4. Stenosis in superficial femoral artery with a gray-scale median of 6 before angioplasty. Anterior plaque = 4.31 mm, minimal luminal diameter = 1.14 mm, and peak systolic velocity ratio = 2.85.

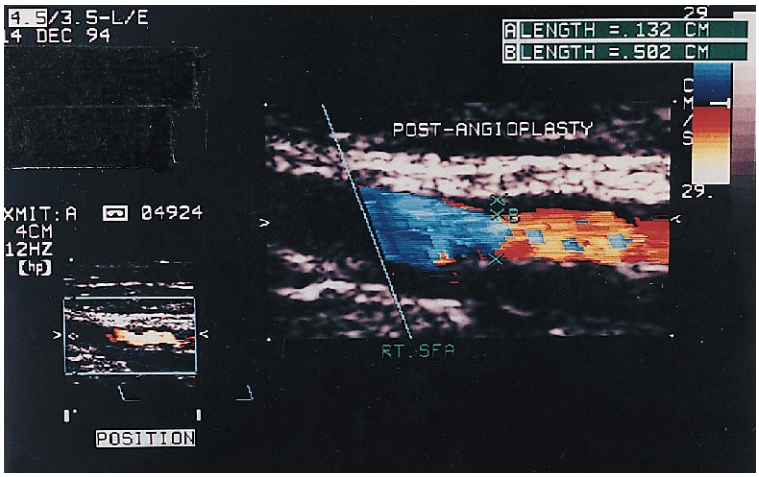

Fig 5. Stenosis shown in Fig 4 on day 1 postangioplasty. Anterior plaque = 1.32 mm (absolute reduction in thickness = 2.99 mm), minimal luminal diameter (MLD) = 5.02 mm (absolute increase in MLD = 3.88 mm), and peak systolic velocity ratio (PSVR) = 1.03 (percent decrease in PSVR = 64%).

stenosis with the highest GSM (71) could not be successfully dilated and showed evidence of restenosis on day 1 after angioplasty.

There was no correlation between GSM and absolute plaque "growth."

DISCUSSION

B-mode ultrasound imaging has been used as a means of characterizing carotid artery bifurcation disease, and its ability to distinguish between fibrous plaque and more complex ones containing intraplaque hemorrhage has been described.[2] Plaques were thus classified as homogenous or heterogenous. The homogenous plaque was defined as having a uniform appearance of high- or medium-level echoes, which signify a large amount of fibrous tissue. In contrast, heterogenous plaques were defined as having discreet bright and dark areas, because they contain lipid deposits and hemorrhage. Other authors[1] have correlated plaque character with symptoms and found heterogenous plaques to be associated with more neurological events than homogenous ones. It has been

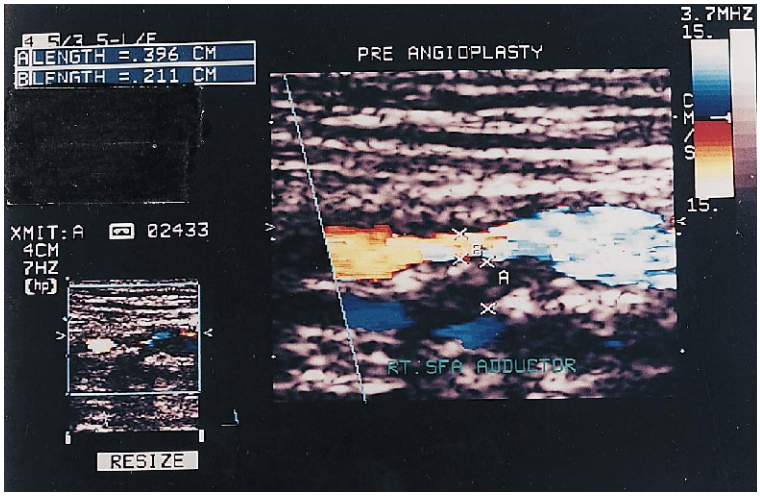

Fig 6. Stenosis in superficial femoral artery with a gray-scale median of 35 before angioplasty. Posterior plaque = 3.96 mm, minimal luminal diameter = 2.11 mm, and peak systolic velocity ratio = 2.46.

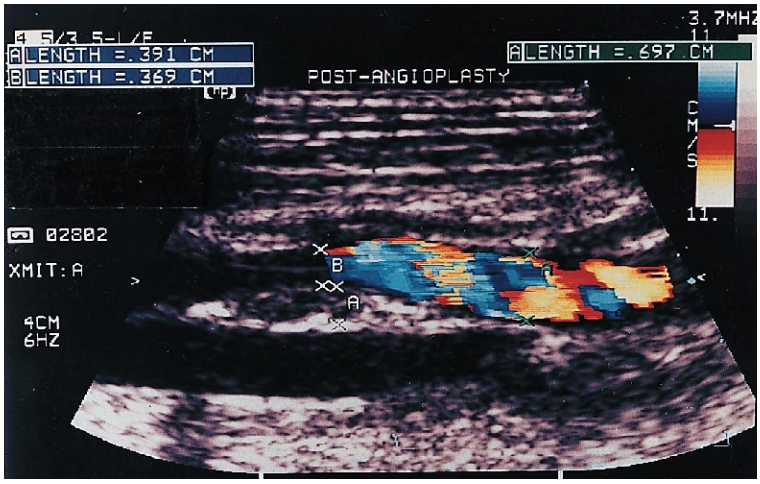

Fig 7. Stenosis shown in Fig 6 on day 1 postangioplasty. Posterior plaque = 3.91 mm (absolute reduction in thickness = 0.05 mm), minimal luminal diameter (MLD) = 3.69 mm (absolute increase in MLD = 1.58 mm) and peak systolic velocity ratio (PSVR) = 1.77 (percent decrease in PSVR = 28%).

shown that echolucent plaques (black on B-mode imaging) are associated with a higher content of lipids and cholesterol and occur more frequently in symptomatic patients; in contrast, echogenic plaques (white on B-mode imaging) contain a larger amount of fibrous tissue and are common in asymptomatic patients. This is probably because echolucent plaques with their high lipid content are more prone to rupture and embolization than echogenic plaques with their higher content of fibrous tissue and calcium. Other publications[3,4] have reported a higher incidence of symptoms (transient ischemic attacks [TIA] and stroke) in echolucent plaques than in echogenic plaques. Ultrasound has also been used as a means of studying the progression of disease and restenosis in carotid arteries after endarterectomy.[8] The assessment of carotid plaque characteristics by means of ultrasound has led to a greater understanding of the natural history of carotid artery disease and the identification of high- and low-risk patients.

The main problem, however, with plaque character assessed by means of ultrasound is that the

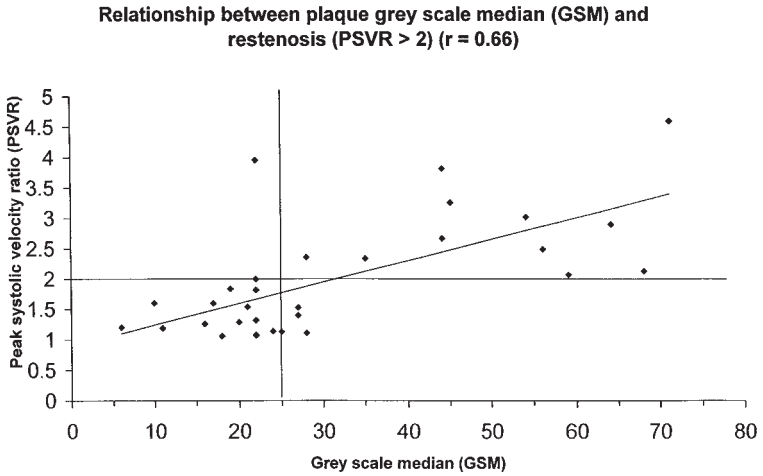

Fig 8. Relationship between plaque grey-scale median (GSM) and peak systolic velocity ratio (PSVR) in the postangioplasty period.

echogenicity and texture of the plaque may be altered by instrument settings for power, dynamic range, gray scale, etc. It is thus subjective and operator-dependent. Recent evidence[5,6] has suggested that computer-based assessment of plaque characteristics would provide a more objective and quantitative, operator-independent method of analysis of plaque echolucency or echogenicity and would probably be more accurate for the diagnosis of plaques at risk of rupture and embolization. However, until normalization of images is achieved, the reproducibility of this method from center to center is in doubt.

Intravascular ultrasound (IVUS) is now recognized as a high-resolution imaging modality and is increasingly being used as a means of guiding the angioplasty, atherectomy, and stenting procedure in coronary and peripheral arteries.[9–18] The experience of imaging with IVUS has shown that it provides a level of detail of plaque morphology that is unattainable with angiography. By means of the 40 MHz IVUS in vitro, 4 basic plaque components have been described:[11] (1) echolucent, composed of lipid deposits; (2) soft echoes, composed of fibromuscular tissue, intimal proliferation, and varying amounts of diffusely dispersed lipids; (3) bright echoes, composed of collagen-rich fibrous tissue; and (4) bright echoes with acoustic shadowing, composed of calcified tissue. IVUS (30 to 40 MHz catheters are used for imaging coronary arteries; 12 MHz catheters are used for imaging peripheral arteries) has been used as a means of deciding on the appropriate treatment strategy. In one report, preinterventional IVUS was performed in 301 patients with 313 target lesions, in the coronary arteries, to determine the appropriate treatment strategy.[13] Based on the IVUS findings, the treatment strategy that was initially formulated on the basis of angiographic findings was changed in 40% of patients, because of newly diagnosed severe lesions, lesion composition assessment leading to a change in revascularization strategy, etc. Another study[14] reported similar findings, in which IVUS findings led to a change in the interventional strategy in nearly 48% of cases. Additionally, in another study, atherosclerosis was detected in more than 90% of angiographically normal, coronary artery reference segments by means of IVUS.[15] IVUS has been used as a means of predicting adverse outcome after coronary angioplasty and the correlation of plaque morphology with angiography, clinical syndrome, and procedural results.[10] It has also been used as a means of determining the presence, magnitude, location, and distribution of calcium within the lesion and has been compared with coronary angiography findings[16]; in this study, calcium was detected by means of angiography in only 38% of lesions, whereas calcium was detected by means of IVUS in nearly 73% of cases. These findings have been corroborated by other authors, who have found that angiography has only a 40% sensitivity in the detection of calcification diagnosed by means of IVUS [17]. IVUS-based studies in coronary arteries have also shown that the location of calcium within the lesion affects outcome, based on the revascularization procedure that is chosen. For instance, rotational atherectomy has been shown to be superior to directional atherectomy for treating fibrocalcific dis-

ease, especially when calcium is located at the luminal surface.[18] On the other hand, if calcium is located deep within the lesion, directional atherectomy may be useful; the softer fibrous plaque may be removed safely, and the calcium that is located deep within the lesion prevents the cutter from entering the media, which may result in perforation. Although IVUS is a useful periprocedural tool for the vascular interventionist, its main drawback is that it is invasive and, therefore, cannot be repeated at frequent intervals.

In this study, all ultrasound images were normalized with a GSM of 0 to 5 for blood and 180 to 190 for adventitia. The correlation between 2 observers for the measurement of plaque GSM was excellent ($r = 0.93$), with the 95% limits of confidence between –4.1 and 5.9.

Balloon angioplasty works by means of the mechanism of plaque fracture, with extension of a dissection plane into the muscular medial wall. The relationship between plaque GSM and absolute decrease in plaque thickness on day 1 was significant ($P < .03$). The lower the plaque GSM, the more effective the process of plaque compression with the angioplasty balloon. This could be explained on the basis of plaques with a GSM less than 25 being more echolucent because of their higher content of cholesterol and, therefore, more compressible than plaques with a GSM greater than 25 because of their higher content of fibrous tissue. There was no correlation between GSM and absolute increase in MLD or percent fall in PSVR on day 1 after angioplasty. This could be explained on the basis that, irrespective of the nature of the plaque, angioplasty achieved its effect, by means of compression in echolucent plaques (GSM less than 25) or, in cases in which the plaque is fibrous and incompressible (GSM more than 25), by means of vessel wall dilatation.

Plaque GSM played an important role in the long-term outcome after angioplasty; in plaques with a GSM greater than 25, the restenosis rate was 78%, in comparison with 12% in those with GSM less than 25 ($P < .001$). When GSM was greater than 30, the restenosis rate was 100%. Indeed, in a very calcified lesion with a GSM of 71, restenosis occurred on day 1 after the procedure. By 6 weeks, 55% of lesions with GSM greater than 25 restenosed. However, there was no correlation between plaque GSM and absolute plaque "growth." One possible explanation is the combination of "growth" and vessel wall recoil in plaques with GSM greater than 25 (because angioplasty worked in these cases by vessel wall dilatation) led to lumen loss and restenosis.

None of the patients in our study had stenting of the arteries after angioplasty. The Dutch Iliac Stent Trial Group[19] recently published the results of a study comparing primary stent placement vs primary angioplasty followed by selective stent placement for patients with iliac artery occlusive disease. Selective stenting was performed if angioplasty alone revealed a residual mean pressure gradient of more than 10 mm at the treated site. This study found no differences in treatment strategies both at short-term and long-term follow-up. The investigators concluded that because selective stent placement is less expensive, it is a better option than direct stent placement for the treatment of iliac occlusive disease. However, this finding cannot be applied to our experience, because of the small numbers in our study and also because the diagnosis of restenosis was based on an increase in the Duplex criterion of PSVR of more than 2 at the site of angioplasty and not on recurrence of patient symptoms.

An important finding in this study was a high rate of restenosis after balloon angioplasty alone in lesions with a high GSM. Therefore, the selection of lesions for angioplasty, based on plaque GSM, could have better therapeutic results. In the case of a calcified lesion with a very high GSM of 71, it could not be dilated adequately by means of balloon angioplasty alone and showed restenosis (PSVR more than 2) on day 1 after angioplasty. The assessment of plaque GSM before the procedure will help the interventionist plan the appropriate treatment strategy. For lesions with a low GSM, balloon angioplasty alone will suffice. However, for fibrocalcific lesions with a high GSM, adjunctive procedures may be needed. Although it is outside the scope of this paper to discuss the best treatment strategies, angioplasty followed by stenting or atherectomy and stenting would seem logical choices.

Additionally, the identification of a high-risk group in patients undergoing angioplasty will be beneficial for future studies in which pharmacological agents aimed at reducing restenosis are tested; because the prevalence of restenosis will be high, the numbers needed to demonstrate the expected difference may be small.

Future studies with larger series of lesions assessed on the basis of ultrasound are needed to lead to a better understanding of the mechanisms involved. The cutoff point of a GSM of 25 should be assessed prospectively in further studies. Also, future studies should correlate ultrasonic plaque characteristics with histological specimens in lesions that have restenosed; this could provide insight into the histo-

logic elements that contribute to restenosis and their associated ultrasonic characteristics.

We thank Pfizer Central Research (Sandwich, United Kingdom) for a research grant to the Imperial College School of Medicine, London, UK, and Jane Harness, MS, for assistance with data collection.

REFERENCES

1. 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;104:652-60.
2. 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.
3. Bock RW, Gray-Weale AC, Mock PA, App-Stats M, Robinson DA, Irwig L, et al. The natural history of asymptomatic carotid artery disease. J Vasc Surg 1993;17:160-71.
4. Geroulakos G, Ramaswami G, Nicolaides A, James K, Labropoulos N, Belcaro G, et al. Characterization of symptomatic and asymptomatic carotid plaques using high-resolution real-time ultrasonography. Br J Surg 1993;80:1274-7.
5. el-Barghouty N, Geroulakos G, Nicolaides A, Androulakis A, Bahal V. Computer-assisted carotid plaque characterization. Eur J Vasc Endovasc Surg 1995;9(4):389-93.
6. el-Barghouti N, Nicolaides AN, Tegos T, Geroulakos G. The relative effect of carotid plaque heterogeneity and echogenicity on ipsilateral cerebral infarction and symptoms of cerebrovascular disease. Int Angiol 1996;15:300-6.
7. Ramaswami G, Dhanjil S, Nicolaides A, Griffin M, Al-Kutoubi A, Tegos T, et al. Restenosis after percutaneous transluminal angioplasty. Am J Surg 1998;176:102-8.
8. Kieny R, Seiller C, Petit H. Evolution of carotid restenosis after endarterectomy. Cardiovasc Surg 1994;2:555-60.
9. Tobis JM, Mallery J, Mahon D, Lehmann K, Zalesky P, Griffith J, et al. Intravascular ultrasound imaging of human coronary arteries in vivo. Circulation 1991;83:913-26.
10. Hodgson JM, Reddy KG, Suneja R, Nair RN, Lesnefsky EJ, Sheehan HM. Intracoronary ultrasound imaging: Correlation of plaque morphology with angiography, clinical syndrome, and procedural results in patients undergoing coronary angiography. J Am Coll Cardiol 1993;21:35-44.
11. Gussenhoven WJ, Essed CE, Lancee CT. Arterial wall characteristics determined by intravsacular ultrasound imaging: An in-vitro study. J Am Coll Cardiol 1989;14:947-52.
12. Scoccianti M, Verbin CS, Kopchok GE, Back MR, Donayre CE, Sinow RM, et al. Intravascular ultrasound guidance for peripheral vascular interventions. J Endovasc Surg 1994; 1:71-80.
13. Mintz GS, Pichard AD, Kovach JA, Kent KM, Satler LF, Javier SP, et al. Impact of preintervention intravascular ultrasound imaging on transcatheter treatment strategies in coronary artery disease. Am J Cardiol 1994;73:423-30.
14. Nishioka T, Luo H, Tabak S, Lepor N, Eigler NL, Forrester JS, et al. The evolving utility of intracoronary ultrasound. J Am Coll Cardiol 1995;75:539-41.
15. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: An intravascular ultrasound study with clinical correlations. J Am Coll Cardiol 1995;25:1479-85.
16. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuany YC, et al. Patterns of calcification in coronary artery disease: A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. Circulation 1995; 91:1959-65.
17. Tuzcu EM, Berkalp B, Moliterno DJ, Goormastic M, De Franco AC, Nissen SE. Can angiography reliably detect and quantify coronary calcification? A comparative intravascular ultrasound study. Circulation 1994;90:I-277.
18. Mintz GS, Potkin BN, Keren G, Satler LF, Pichard AD, Kent KM, et al. Intravascular ultrasound evaluation of the effect of rotational atherectomy in obstructive atherosclerotic coronary artery disease. Circulation 1992;86:1383-93.
19. Tetteroo E, van der Graff Y, Bosch JL, van Engelen AD, Hunink MGM, Eikelboom BC, et al. Randomized comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Lancet 1998;351:1153-9.

Submitted Jun 11, 1998; accepted Aug 11, 1998.

DISCUSSION

Dr R. Eugene Zierler (Seattle, Wash). Although the degree of stenosis produced by an atherosclerotic plaque has traditionally served as both the principal indicator for intervention and the means for assessing the clinical outcome, there are other features of plaques that may be important. Examples of such features include ulceration, hemorrhage, and calcification. However, attempts to identify plaque histology based on B-mode ultrasound have met with variable success.

The study of atherosclerotic lesions by means of ultrasound is difficult, because of the many technical issues that are involved in producing the images and the lack of any standardized criteria for their interpretation. Thus, plaque characterization by means of ultrasound has been too subjective and qualitative to be useful in the clinical setting.

In fact, our group in Seattle has shifted from ultrasound to other approaches, such as MR imaging, for plaque characterization. However, in an effort to obtain a more objective and quantitative assessment of plaque features, the group at St. Mary's Hospital has developed a computer-assisted ultrasound technique that relies on the gray-scale median as a measure of overall plaque echogenicity. This technique was first described in 1995 and until now has been applied primarily to the characterization of carotid artery plaques.

This paper by Ramaswami and colleagues extends the application of this computer-assisted technique from the

carotid to the peripheral arteries. They found that relatively echolucent lesions with a gray-scale median less than 25 had a significant reduction in plaque thickness immediately after angioplasty, compared with more echogenic lesions. Similarly, the restenosis rate was only 12% when the gray-scale median was less than 25, in contrast to 79% for lesions with a gray-scale median greater than 25. When the gray-scale median was greater than 30, the restenosis rate was 100%.

The results of this study suggest that the outcome of balloon angioplasty can be predicted based on plaque echogenicity as measured by means of the gray-scale median. If this is true, then such a technique could be used to select patients for intervention and to identify those patients who might benefit from adjunctive mechanical or pharmacologic therapies. However, as the authors point out, this approach must be validated prospectively.

I would like to pose the following questions to Dr. Ramaswami and his coauthors.

First, because this study included 31 stenoses in 17 patients, it is obvious that many of the patients had more than 1 lesion treated. In this situation, multiple lesions in a single patient are subject to the same general risk factors for restenosis. Therefore, the risk of restenosis in these lesions is not truly independent. There are statistical methods for dealing with these circumstances, but it is not clear that such methods were used in your analysis. Do you have any data on the role of patient factors such as sex, smoking, or diabetes on the outcome of balloon angioplasty in your study?

Second, the results of balloon angioplasty tend to be better in the iliac than the more distal arterial segments. Was there any difference in gray-scale median or other predictive parameters based on location of the lesion (for example, the common or external iliac, compared with the superficial femoral arteries)?

Finally, severe plaque calcification is quite common in peripheral atherosclerotic lesions and produces acoustic shadowing with loss of gray-scale information from the deeper tissues. How is this situation dealt with in determining the gray-scale median by the computer-assisted technique?

I compliment the authors on this interesting study and appreciate the opportunity to discuss it.

Dr Ganesh Ramaswami. Thank you, Dr. Zierler. In this group, there were 31 stenoses in 17 patients. We looked at the risk factors of sex, smoking, diabetes, hypercholesterinemia, and hypertension and found no difference between the lesions that restenosed and the ones that did not.

I would like to reiterate here that the restenosis criterion that we used for the study was an increase in the peak systolic velocity ratio to more than 2.0 at the site of angioplasty, and not the recurrence of symptoms associated with a fall in ankle brachial indices during the postangioplasty period.

In answer to your second question, the gray-scale median of the iliac lesions averaged 29, and the gray-scale median of the femoropopliteal lesions averaged 32. There was no significant difference in the gray-scale median between these lesions.

About your third question on the role of plaque calcification and how that would interfere with the measurement of the gray-scale median, if plaque calcification produced acoustic shadowing, measurements of the plaque gray-scale median cannot be done. On the other hand, if there was calcification that did not produce significant shadowing, the gray-scale median could still be measured.

I would like to add that the presence of calcium in the plaque would increase the gray-scale median of the lesion.

Dr Alexander W. Clowes (Seattle, Wash). One of the things that I noted in your presentation was that you are very careful not to describe the mechanism of stenosis or restenosis. We now know by means of intravascular ultrasound that angioplasty restenosis is largely caused by pathological remodeling, a form of shrinkage, and not by intimal hyperplasia, whereas in the stent it's caused by intimal hyperplasia. Do you have any information about the mechanism of restenosis? And do you think that the observations you have made will predict restenosis inside a stented vessel and inside an angioplastied vessel?

Dr Ramaswami. Measuring plaque thickness in the stented vessel may not be that easy, because the stent metal may cause echo reverberations in the proximal wall. We did not have any patients who were stented in this group. They all underwent balloon angioplasty.

I do agree that there are other mechanisms involved in the restenotic process. Because this study was with transcutaneous ultrasound, we measured plaque gray-scale median and correlated this with plaque thickness, minimal luminal diameter, and peak systolic velocity ratio changes in the postangioplasty period. All that we can say is there was a higher restenosis rate in the group with the higher gray-scale median. This could possibly be caused by fibrous plaques being incompressible and the mechanism of angioplasty in these lesions, purely by stretching the vessel wall, so the component of plaque growth followed by vessel wall recoil in this group led to a higher rate of restenosis.

Dr Samuel S. Ahn (Los Angeles, Calif). I congratulate the authors for bringing to our attention a potentially useful way to better select patients for balloon angioplasty, but I have 2 issues to raise. First, how did you come up with your criterion for restenosis? You used a peak systolic ratio greater than 2.0 as a restenosis rate. In my own practice, I'm not sure exactly what criteria we should use for saying whether that restenosis is significant. Furthermore, how does that peak velocity ratio of 2.0 correlate to ankle-arm index, exercise ankle-arm index, the patient's symptoms, etc.?

The second issue regards your comments about possibly stenting those patients with the higher density echogenicity. Stents do not necessarily prevent restenosis. There is no good data that supports using stents in this situation.

Dr Ramaswami. Thank you, Dr. Ahn. In answer to your first question about the peak systolic velocity ratio of 2.0, we used that because it's a well-established criterion signifying more than 50% reduction in diameter. All these lesions had the peak systolic velocity ratio (PSVR) measured before the procedure, and the PSVR was less than

2.0 immediately after angioplasty. We took an increase in the PSVR to more than 2.0 to indicate restenosis, because this would mean that the lesion had recurred. But this was not symptomatic restenosis. In a proportion of the patients, the peak systolic velocity ratio increased to more than 2.0, despite patients being asymptomatic and also the ankle brachial index showing no fall.

Regarding your second question about stenting, because this group underwent balloon angioplasty with restenosis that we could predict on the basis of the gray-scale median, we proposed that stenting could be a better procedure to keep these vessels open, because angioplasty achieved its effect in these lesions with a high gray-scale median purely by stretching the vessel wall, rather than compressing the plaque. I do agree with you that stents do not necessarily prevent restenosis. Perhaps we should consider other procedures, such as atherectomy, in fibrocalcific lesions with a high gray-scale median as an adjunct procedure to balloons and stenting.

Dr Ross Lyon (New York, NY). I greatly enjoyed your paper.

My question relates to other characteristics, morphologic characteristics, of plaque. There certainly may be other characteristics that are important in determining the effectiveness of balloon angioplasty. Did you look at plaque circumference of the arterial wall? Also, did you look at plaque length? And if you did, what did you find?

Dr Ramaswami. Thank you. Transverse section imaging of these arteries is suboptimal, so we had to go purely by the longitudinal images. We do realize that with longitudinal measurements we still miss the plaques on the side of the artery, but we made sure that we were at the same site in every instance, we got the maximum thickness of the anterior and the posterior component of the plaque, and this was used to calculate the gray-scale median, the changes in plaque thickness, minimal luminal diameter, and peak systolic velocity ratio during follow-up. We did not calculate plaque circumference. Also, these lesions were less than 5 cm long.

Dr Sergio X. Salles-Cunha (Toledo, Ohio). I am curious about the complexity of the plaque. Was there any additional information in the variance, standard deviation, or the histogram of the echo measurements?

Dr Ramaswami. We did not take the mean, we took the median, because the histogram was skewed. And so, the gray-scale median of the pixels of the histogram was used as a measure of plaque echodensity. We did not measure the variance of the standard deviation.

Dr Salles-Cunha. So, did you study that histogram? Was there any additional information, if the histogram was wide or narrow?

Dr Ramaswami. Yes, if the histogram was wide, it meant that the plaque had both echolucent and echogenic areas. That meant the spread of the histogram was broader. In comparison, if you had a purely echolucent plaque, then the spread of the histogram was narrower.

Dr Christopher K. Zarins (Stanford, Calif). I wonder if you could explain to me the concept of plaque compression. Is it possible to compress a solid, a liquid, or both?

Dr Ramaswami. Well, plaque volume remains constant. Looking at the images that we had of echolucent plaques immediately after the angioplasty, we saw that the angioplasty balloon flattens out the plaque and spreads it axially across the length of the vessel. So, there was a significant decrease in the plaque thickness that we could measure by means of ultrasound, and this we referred to as plaque compression.

Dr Zarins. But you're not actually compressing the plaque, you're redistributing it; you're flattening it, not actually compressing it.

Dr Ramaswami. Yes, in comparison with the echogenic fibrous plaques that are incompressible. So, there is no decrease in the plaque thickness, but angioplasty still achieves its effect by stretching the vessel wall.