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Preoperative B-mode ultrasound plaque appearance compared with carotid endarterectomy specimen histology

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In carotid artery stenosis both the degree of the lesion and its plaque morphology are thought to be associated with the carrier's thromboembolic risk. In this study we evaluated the diagnostic preciseness of non-invasively B-mode ultrasound in predicting the histopathological plaque structure. We examined 44 patients with $>50\%$ ICA stenosis by B-mode within 6 weeks prior to carotid endarterectomy. At the affected bifurcations, up to 10 different regions of interest (ROI) per artery were investigated. Plaque appearance was classified according to 6 subtypes considering different ultrasonic plaque features. Postoperatively, plaque specimens were examined histopathologically for their relative content of calcification, fibrous tissue and different soft tissue. B-mode ultrasound was compared with histopathological features in ROI. A total of 265 regions of interest were evaluated. In mainly echolucent types of plaques, atheromatous debris was most frequently seen, whereas fibrosis was rare. Homogeneous echolucent plaques showed a high proportion of cholesterol and/or recent haemorrhage. Thrombosis at the plaque surface was often seen in "completely echolucent" plaque type (each $P<0.001$). Carotid B-mode ultrasonography is able to predict the histopathological components and the texture of carotid plaques.

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Atherosclerotic disease of the carotid bifurcation causes ischaemic stroke mainly by arterio–arterial embolism (1, 2). Apart from the degree of carotid artery stenosis, the presence of intraplaque haemorrhage, irregular plaque surface and fissures or craters within a plaque are thought to be indicators of a high thromboembolic risk (3–6). B-mode ultrasound permits to non-invasively identify carotid artery plaques and to characterize plaque's surface, its integrity and the intraplaque structure (7). Several investigators suggested that plaques exhibiting a "homogeneous dense" appearance are "stable" and are correlated with a low risk of subsequent ischaemic events. On the other hand, heterogeneous or even completely echolucent plaques have been associated with a high risk of ischaemic neurological events. The pathomorphologic correlate to these ultrasound features was found to be either high content of lipids or intraplaque haemorrhage, whereas the "stable" plaque mainly consists of fibrous or calcificated tissue (8–10).

Other investigators could not establish a reliable correlation between ultrasonic and histopathological findings particularly not with intraplaque haemorrhage and ulceration (11, 12).

The correlation between sonographic characteristics, histological findings and the clinical outcome is still under discussion (13–15), however, since the ultrasound technology is permanently improving.

We used a refined spatial analysis of the lesions by a multiplane subdivision of the plaques at the carotid bifurcation. We compared the pre-operative B-mode ultrasound appearance with the tissue composition of the endarterectomy specimen. To obtain information about the relative tissue components in different plaque types, we determined the histological findings semiquantitatively.

Methods

We investigated 46 carotid endarterectomy specimens derived from 44 patients (30 males, 14 females, mean age 58.4 years). Forty-one patients had experienced cerebral or retinal ischaemic events in the corresponding vascular territory. Three patients were asymptomatic but had experienced a rapid progression of their ICA stenoses to high-grade lesions during repetitive ultrasounds checks. The prevalence of cardiovascular risk factors (arterial hypertension, hyperlipidaemia, diabetes mellitus, current smoking, adipositas and coronary sclerosis) was assessed taking into account the patients' history, as well as the clinical and laboratory findings evaluated during their stay in hospital. The B-mode ultrasound examination was performed within 6 weeks (mean 11.0 days) prior to the endarterectomy. Sonographic plaque appearance was categorized as follows (7) (Fig. 1):

IMT: intima media thickening, by 1 to 2 mm (per definitionem, thickening over 2 mm was called a plaque)

Type I: echogenic, homogeneous plaque with a regular surface

Type II: predominantly echogenic plaque with a sporadically disrupted surface

Type III: predominantly echolucent, heterogeneous (heterogeneous means complex echo patterns within all layers of the plaque) plaque with an irregular surface

Type IV: echolucent, homogeneous plaque with a difficult to delineate surface

Type V: completely echolucent with a continuous surface

Type VI: echogenic and homogeneous plaque with speckles leading to ultrasonic showing

(Type I to V represents soft plaques, while type VI is a calcificated soft plaque).

According to Crouse et al. (16) the carotid artery bifurcation was subdivided into 5 axial segments of 5 mm thickness (from 10 mm below the flow divider up to 5 mm above it). The sonographically medial and lateral, i.e. the near and far wall of the distal common carotid (CCA) and the internal carotid artery (ICA), respectively, were investigated (10 regions of interest per vessel, Fig. 2). Additionally, each plaque was divided into 3 longitudinal layers (near intimal, middle and far intimal layer). The carotid arteries were sonographically investigated in the longitudinal and transverse plane using a real-time-scanner – Biosound 2000 SA with an 8 MHz (6–10 MHz) mechanical transducer. The axial resolution was 0.3 mm and the lateral resolution was 0.7 mm at the focal point. The two-dimensional image display provided 60 image frames per s and it displayed 256 grey levels. The disadvantage of the device was its large and heavy probe not allowing to image patients with a distally located ICA bifurcation. Firstly, the transducer was positioned longitudinally and scanning was performed from an antero–lateral approach, while the transducer was placed between the trachea and the sternocleidomastoid muscle. Subsequently, the patient rotated the head exactly 45 degrees to the contralateral side and the transducer was positioned on the sternocleidomastoid muscle. In order to obtain transverse scans the transducer was turned to 90 degrees keeping the patient's head position constantly. Two experienced investigators (E.B.R. and N.H.) have performed all B-mode ultrasound examinations. The investigations were recorded on videotape and revised by both ultrasonographers. Conflicting results were discussed to achieve an agreement.

During endarterectomy the patient's head was rotated 45 degrees contralaterally and surgeons always performed the incision and exposition of carotid bifurcation in the same way: Along the ventral edge of the sternocleidomastoid muscle an oblique incision was done. The muscle and the remaining tissue were pushed dorsolaterally and the carotid trunk was exposed. In accordance to this constant incision, the near semicircle of the vessel was declared as sonographically lateral and the far semicircle as sonographically medial, respectively. Each surgical specimen was obtained en bloc.

Histological examination

Postoperatively, each specimen was fixed in 10% formaldehyde and decalcified in Planck solution when necessary. After fixation (and decalcification) the specimens were cut transversely in 3–4 mm thick slices. The cross-slices were placed according to the axial ultrasound planes. Serial cross sections (5–10 µm) were obtained throughout the whole length of the plaque. Sections from all segments were stained with haematoxylin/eosin and were roughly quantified for fibrosis, atheroma containing fatty necrotic debris, cholesterol crystals, recent or old haemorrhage, thrombosis, calcification and granulation tissue.

An experienced pathologist (L.F.) blinded for the result of the ultrasonographic examination analysed the sections semiquantitatively. He estimated the proportion of the above-mentioned tissue components within the lesion as follows: 0 = absent, i.e. 0–$\leq$1%; 1 = little, i.e. $>$1%–$\leq$10%; 2 = moderate, i.e. $>$10%–$\leq$33%; 3 = much, i.e. $>$33%.

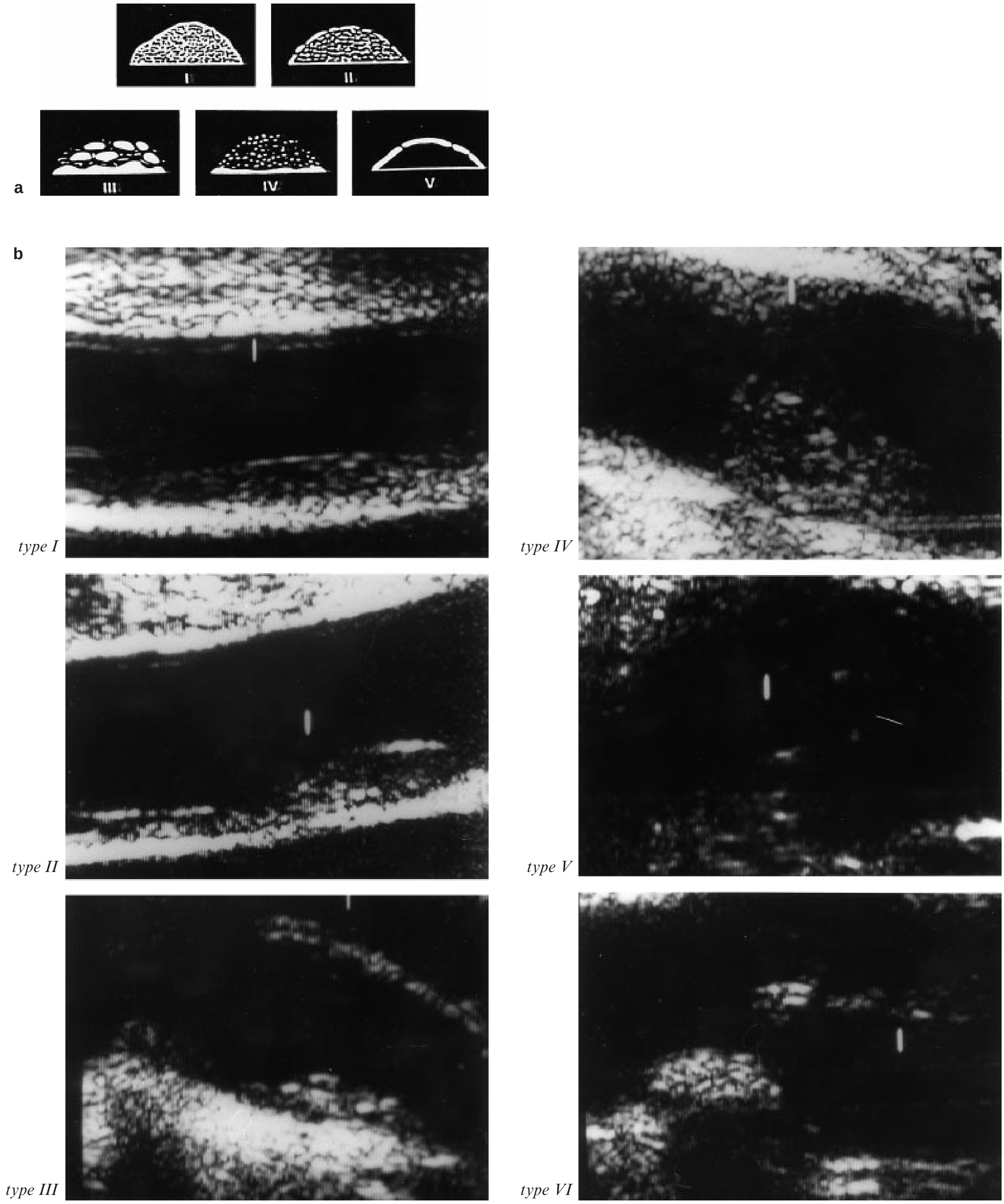

Fig. 1a,b. a) Diagrammatic representation of the morphology of the ultrasonic soft plaque types I–V (7). b) Representative B-mode ultrasound images of soft plaque types I–V and calcificated soft plaque (type VI). Type I: Homogeneous echogenic soft plaque with nearly continuous surface. Type II: Predominantly echogenic, rather homogeneous soft plaque with a sporadically disrupted surface. Type III: Inhomogeneous, moderately echogenic soft plaque with some intensely bright internal plaque patterns. Type IV: Predominantly homogeneous and echolucent soft plaques at both vessel walls. Type V: Homogeneous, nearly anechoic soft plaques at both vessel walls. The surface is partially visible. Type VI: Moderately homogeneous, echogenic calcificated soft plaque. Ultrasonic shadowing obscures deeper surfaces below the plaque.

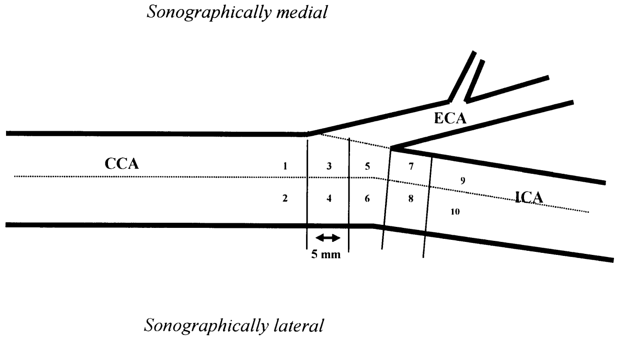

Fig. 2. Drawing of the carotid bifurcation showing the 10 segments studied sonographically and histologically.

We also investigated the diagnostic value of the ultrasonic plaque features concerning echogenicity, plaque surface and intraplaque composition. The degree of ICA stenosis was classified by cw-Doppler sonography with frequency analysis according to Widder (17).

Statistical analysis

We used the chi-square test and Fisher's exact test to compare the pathological and ultrasonic findings. If there was a correlation, we used Cramer's V-Test (values between −1 and 1) to describe the strength of this relation (18). Also, the sensitivity and specifity of B-mode scan to predict the histological findings were assessed.

Results

The degree of ICA stenosis was >50–80% in 14 cases and >80% in 32 cases, respectively.

A total of 265 regions of interest (mean 5.8 per specimen) were evaluated. Every region of interest consisted of 3 longitudinal layers, respectively, such that a total number of 795 segments were assessed by both ultrasound morphology and histopathology. No correlation between ultrasonic plaque type and vascular risk factors, degree of ICA stenosis or previous neurological symptoms was found. Plaque types III, IV, V and VI were seen much more frequently in the ICA segments than in the bulb ($P<0.001$) or in the CCA segments.

Table 1 provides the association of the various histological features with different plaque types during ultrasound. Fatty necrotic debris was predominantly seen in types III, IV and V, whereas fibrosis was only rarely present in these plaques. In addition, type IV showed a high proportion of cholesterol crystals and recent haemorrhage. Calcification was mostly observed in plaque types III and VI.

Table 2 shows the sensitivity and specificity of the histological versus ultrasonographical findings. Plaque type II could highly specifically be identified by ultrasound because of its characteristic composition of fatty necrotic debris, cholesterol and fibrosis. The sensitivity of the histological features to predict certain ultrasound types of plaque was low. However, the ultrasound type IV of plaques showed a good sensitivity to identify a moderate proportion (>10%) of cholesterol or recent haemorrhage.

We correlated ultrasonic plaque features (plaque surface, echogenicity, internal plaque structure) with the presence of histopathological components; the presence of the various plaque constituents was estimated as a percentage of the total tissue composition of the region of interest and was subdivided into two categories (1) ≤10% (2) >10%. Highly significant results are given in the following chapter (each $P<0.001$ Fisher's Exact Test, two-tailed): Echolucent plaque appearance was correlated with a high content of fatty necrotic debris (sensitivity 0.62, specifity 0.76, Cramer's V-test [CVT] 0.439), cholesterol (sensitivity 0.79, specifity 0.51, CVT 0.224) and recent haemorrhage (sensitivity 0.74, specifity 0.51, CVT 0.200). However, fibrosis was strongly associated with echogenic plaque appearance (sensitivity 0.55, specifity 0.86, CVT 0.338).

Furthermore, a difficult-to-delineate, or a clefted or irregular plaque surface was significantly correlated with the presence of fatty necrotic debris (sensitivity 0.62, specifity 0.76, CVT 0.388), recent haemorrhage (sensitivity 0.82, specifity 0.55, CVT 0.267) and thrombosis (sensitivity 0.33, specifity

Table 1. Quantitative distribution of histological findings in different plaque types

Histological finding	IMT	Type 2	Type 3	Type 4	Type 5	Type 6	Chi-square test	Cramer's V-Test
Fatty necrotic debris	+	+	+++	+++	+++	++	$P<0.001$	0.365
Cholesterol	0	+	++	+++	++	+/++	$P<0.001$	0.261
Fibrosis	+++	+++	++	+	+	++	$P<0.001$	0.335
Recent haemorrhage	0/+	+	++	+++	+	+/++	$P<0.001$	0.248
Thrombosis	0	+	++	++	+++	++	$P<0.001$	0.162
Old haemorrhage	0	+	+	++	++	+	$P<0.001$	0.157
Calcification	+	+	++/+++	+	++	+++	$P<0.001$	0.330
Granulation tissue	0	+	+	+	+	+	$P<0.01$	0.123

0 = absent, + = minor, ++ = moderate, +++ = much.

Table 2. Validity (sensitivity and specifity) of the different plaque types to determine the histological composition

B-mode-findings (plaque type)	Histological findings (proportion in %)	Sensitivity	Specifity
Type 2	Fatty necrotic debris $<1\%$	0.63	0.87
Type 2	Cholesterol $<1\%$	0.40	0.92
Type 2	Thrombosis $<10\%$	0.35	0.89
Type 2	Fibrosis $>33\%$	0.50	0.97
Type 3	Calcification $>10\%$ & $<33\%$	0.38	0.92
Type 4	Cholesterol $>10\%$	0.77	0.66
Type 4	Recent haemorrhage $>10\%$	0.76	0.67
Type 4	Fibrosis $<33\%$	0.71	0.68
Type 6	Calcification $>33\%$	0.68	0.94

0.93, CVT 0.299), while a smooth or largely regular (sonographic) surface was predominantly seen in case of a high proportion of fibrosis. A heterogeneous sonographical internal plaque structure was correlated with the histological finding of fatty necrotic debris (sensitivity 0.41, specifity 0.91, CVT 0.363), recent haemorrhage (sensitivity 0.46, specifity 0.80, CVT 0.232) and calcification (sensitivity 0.52, specifity 0.78, CVT 0.214).

Discussion

A recent international consensus meeting at Paris on the ultrasound morphology summarized the state-of-the-art knowledge (19). The risk of cerebral ischaemia is strongly related to the degree of an ICA stenosis; additional factors of an increased risk of stroke are evidence of progression, surface ulceration and low echogenicity (19). In previous studies comparing sonographic and pathoanatomic findings attention was mainly directed to intraplaque haemorrhage and plaque ulceration (3, 11, 12, 20–24). A sensitivity of more than 90% and a specifity ranging from 65 to 88% by B-mode ultrasound for the detection of intraplaque haemorrhage have been reported (9, 22, 23). Sonography's ability to image other important pathological features of atherosclerotic plaques as well has not been investigated systematically. Therefore, we compared the pre-operative B-mode ultrasound appearance of carotid plaque with the endarterectomy specimen considering the proportion of various tissue components.

In our study, the sensitivity of B-mode scanning to estimate the histological composition of atherosclerotic plaques was only moderate (Table 2). One possible reason may be that we used as many as 8 different tissue components to be evaluated. Moreover, and different from previous studies, we even quantified the proportion of the various plaque components semiquantitatively. Nevertheless, we could demonstrate a strong relation between a heterogeneous sonographic appearance and a high proportion of fatty necrotic debris and recent haemorrhage and (Cramer's V-test: >0.20; Fisher's Exact Test, two-tailed $P<0.001$). In accordance with our results, Gray-Weale et al. (20) found an intraplaque haemorrhage in 83% of the heterogeneous lesions, Bluth et al. (22) in 81%. However, Droste et al. (11) detected atheroma with haemorrhage only in 4 out of 9 lesions with an inhomogeneous texture on ultrasound. Echogenic homogeneous lesions were found to contain regularly a high proportion of fibrotic changes in our study. This finding was consistent with that of Bluth et al. (22) and Reilly et al. (9). O'Donnell et al. (24) noticed an increasing echogenicity according to the content of fibrous tissue, while echogenic speckle within echolucent lesions mostly reflected the presence of lipids or intraplaque haemorrhage.

Since no single histological component can reliably be predicted by means of ultrasonic plaque features on an individual basis, carotid lesions have to be labelled with the ultrasonographic nomenclature (7, 20, 25). The proposed subdivision into 6 plaque types considering the ultrasonic plaque features echogenicity, surface and texture, was in accordance with the variability of the histopathological findings: Fatty necrotic debris, cholesterol and thrombosis were seen predominantly in the echolucent plaque types (i.e. types III, IV and V). A high proportion of recent haemorrhage was detected in type IV. Moreover, a clefted or irregular, or a difficult-to-delinate plaque surface was strongly associated with the presence of fatty necrotic debris, thrombosis and recent haemorrhage (each $>10\%$ of the total plaque composition). Another current four-step classification of plaque structure had been introduced by Gray-Weale et al. (20) who expanded their earlier classification (10): Type I, II and III were heterogeneous plaques, while type I and II showed dominantly echolucent feature. Type IV had a uniformly echogenic appearance. The pathological correlation according to this subdivision revealed that 174 of 179 lesions classified as having a type I or II appearance contained intraplaque haemorrhage or were ulcerated. Types III and IV by Gray-Weale et al. showed a predominance of fibrous material. The scheme of plaque characteristics proposed by de Bray et al. (19) is a 5-step semiquantitative classification; the authors pointed out the determination of 2 parameters: The echogenic structure of the lesion (5 classes) and the appearance of the plaque surface (3 classes), while the determination of the texture (homogeneous to heterogeneous) is included in the 5-step classification of the echogenic structure. This classification system allows for a lot of various combinations of the above parameters leading to an exact description of the lesion. However, our classification scheme is confined to a limited number of detailed described plaque types for clinical usage; although considering all sonographical plaque features, it may be possible that a lesion is difficult to classify in individual cases.

Several prospective sonographical follow-up studies on ICA plaques over a mean of 15 to 36 months pointed out that besides the degree of the stenosis both the echolucent and heterogeneous appearance of the lesion was significantly associated with an increased risk of a subsequent cerebral ischaemic event as compared to predominantly echogenic plaques (6, 26, 27). The "unstable", i.e. heterogeneous sonographic appearance of the ICA plaque was found to correspond to either intraplaque haemorrhage, lipids or accumulation of parietal thrombosis (9, 10, 28), all 3 conditions known to have an unfavourable prognosis. Lipid storage and intraplaque haemorrhage are equally unfavourable, which means that ultrasonography's inability to distinguish these conditions is not a major drawback of carotid B-mode imaging (29).

We could confirm that the aforementioned histological findings correlated with a sonographically irregular appearance of the plaque surface. Accordingly, plaque types III, IV and V sonographically and histologically fulfilled the features of an unstable carotid lesion. However, Hatsukami et al. (13) found no difference between plaques removed from asymptomatic and symptomatic patients with regard to the presence and volume of different histological components. In a post mortem study, Svindland & Torvik (30) observed that small recent and old intraplaque haemorrhages and ulcers were a common finding in asymptomatic carotid plaques producing a greater than 60% stenosis. These results show that additional factors other than plaque morphology and degree of ICA stenosis are responsible for the prognosis. Perhaps, the change in plaque appearance over time and/or plaque motion are of great importance.

In conclusion, our findings indicate that high-resolution B-mode imaging of the carotid bifurcation is able to semiquantitatively predict different tissue components of atherosclerotic lesions. This may enable B-mode ultrasound to differentiate stable from unstable plaques which are known to be associated with a high risk of subsequent ischaemic events.

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