Peer reviewed article

Ultrasonographic assessment of the morphological characteristics of the carotid plaque

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Summary

Apart from the degree of stenosis, plaque morphology has emerged in recent years as an important contributory factor in stroke risk. Ultrasound studies have shown that hypo- or anechogenic plaques carry a higher risk of cerebrovascular events than echogenic ones. Similarly, heterogeneous plaques presenting a complex pattern of echogenicity in ultrasound have also been more frequently associated with the occurrence of neurological symptoms than homogeneous lesions. Further, most studies determining the surface characteristics in ultrasound have found that ulceration also predicted increased risk of subsequent stroke. These studies are, however, based on visual evaluation using different classification systems and presenting a high variability of intra- and interobserver agreement. A quantitative method using a computerised image analysis of the plaque based on a grey-scale median (GSM) value has recently been developed which allows a more objective and reproducible evaluation of plaque echogenicity. Several studies have also shown that low GSM values are associated with an increased stroke incidence. A stratified GSM analysis determining the GSM in each one millimeter-thick stratum of the plaque may represent an additional method of determining different components of unstable plaques, such as thinning of the fibrous cap and the position of the necrotic core near the surface.

This article reviews the ultrasonic morphology of the carotid plaque, its clinical prognostic value and correlations with histopathological studies. Recent ultrasound developments in the assessment of plaque echogenicity are also discussed.

Key words: carotid plaque; ultrasonography; echogenicity; grey-scale median

Introduction

Atherosclerosis is a progressive disease characterised by the accumulation of lipids and fibrous elements in the large arteries [1]. The early lesions of atherosclerosis consist of subendothelial cholesterol-engorged macrophages called foam cells. More advanced lesions are characterised by the accumulation of lipid-rich necrotic debris and smooth muscle cells. Fibrous lesions typically have a fibrous cap consisting of smooth muscle cells and extracellular matrix which surrounds and encloses the lipid-rich necrotic core. As the plaque progresses it may exhibit calcifications, ulcerations at the luminal surface and haemorrhaging which is presumed to result from small vessels growing into the lesion from the media of the blood vessel wall [2–4]. The main mechanism of stroke related to pathology of the carotid artery is thought to be embolism from a fissured or ruptured plaque. Recent pathological studies of postmortem and arterectomy specimens have shown that plaque vulnerability is related to the size of the atheromatous core, the thickness of the fibrous cap and inflammation within the cap. Unstable plaques usually have a thin fibrous cap with a necrotic core situated near the surface. The position of the core and the local thinning of the cap may therefore predispose to rupture, which then exposes the thrombogenic atheroma to circulating blood, thus initiating thrombus formation possibly leading to thromboembolism and subsequent ischaemic stroke [2]. Recent multicentre trials have established the benefit of endarterectomy in patients with symptomatic (between 50% and 99%) or asymptomatic (more than 60%) stenosis [5–8]. Overviews of these trials, however, showed that a large proportion of the patients on medical treatment remained free of symptoms during the follow-up period despite the presence of highly stenotic lesions and that, in some rare cases, patients with more moderate degrees of stenosis also experienced neurological events [9]. This suggests that the degree of stenosis alone is not a sufficiently sensitive and specific marker of stroke risk.

No financial support declared.

High resolution ultrasound is a useful tool for characterisation of plaque structure. Most studies performed so far on ultrasonographic plaque morphology agree that anechogenic (weakly reflecting ultrasound) or heterogeneous plaques (presenting with a complex pattern of echogenicity and with at least one hypoechogenic area) carry a higher risk of subsequent neurological symptoms in comparison with echogenic (strongly reflecting ultrasound) or homogeneous ones (plaques with a uniform texture) [10–13]. Further, a few studies determining the surface characteristics of the plaque in ultrasound have found that irregularity and ulceration were also associated with an increased risk of subsequent stroke [14]. All these studies however are based on visual evaluation only, using often very different classification systems and definitions yielding poor inter- and intraobserver agreement. More recently a more quantitative method using computerised image analysis with grey-scale median (GSM) has been developed, allowing a more reliable and quantitative evaluation of plaque structure and its echogenicity [15].

Classifications of carotid plaque morphology by visual analysis

There are 3 main parameters which constitute the basis of plaque morphology classification: plaque echogenicity, texture and surface.

Echogenicity

Ultrasonic tissue characteristics are classified according to the overall distribution of grey tones (overall brightness). Echogenicity varies from anechogenic (dark plaques on ultrasound) through mixed forms to hyperechogenic (bright plaques on ultrasound). It is further defined according to various anatomical structure references. Several classifications of plaque echogenicity have been reported in the literature. Initially, in 1983, Reilly et al. introduced a characterisation of plaque structure into homogeneous (having uniform high or medium level echoes), and heterogeneous (having high, medium and low level echoes) [16]. In 1985 Johnson et al. established three different criteria relating to plaque composition, including calcified, dense (less hyperechogenic than calcified lesions) or soft plaques (isoechogenic in comparison with blood) [17]. In 1988, Gray-Weale discribed 4 different plaque types: Type 1 (anechogenic with echogenic fibrous cap), Type 2 (predominantly anechogenic but with echogenic areas representing less than 25% of the plaque), Type 3 (predominantly hyperechogenic but with anechogenic areas representing less than 25% of the plaque) and Type 4 (echogenic and homogeneous plaque) [18]. In 1990, Widder et al. used a reverse classification, the most anechogenic plaques being assigned to Type IV and .the most echogenic to Type I [19]. Finally, Geroulakos et al. (1993) introduced a modified version of Gray-Weale's classification including a 5th category of unclassified plaque reflecting calcified plaques which may have zones of acoustic shadowing which obscure the deeper part of the arterial wall as well as the vessel lumen [20] (fig. 1). According to a recent consensus meeting on plaque characterisation, echogenicity should be standandised against 3 reference structures: flowing blood for anechogenic, sternocleidomastoid muscle for isoechogenic and the adjacent transverse apophysis of the cervical vertebrae for hyperechogenicity [21]. Some studies further suggested the use of the bright far wall media-adventitia interface as a reference for hyperechogenicity [22].

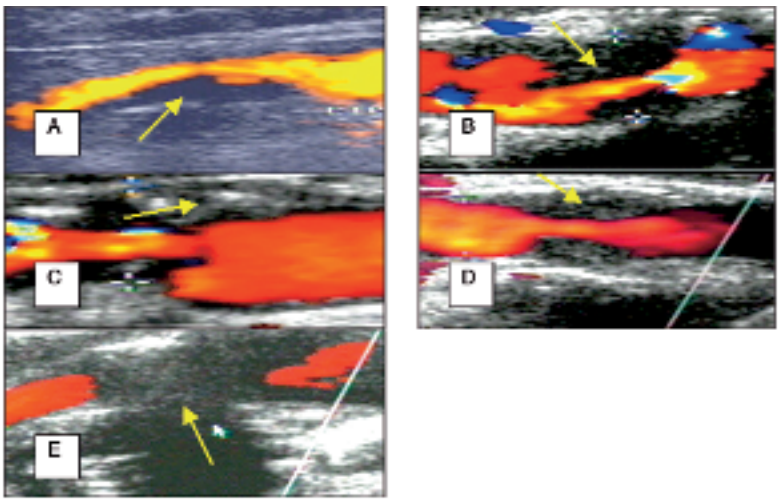


Figure 1

Five different types of plaque according to Geroulakos et al.:
A. Type 1: uniformly echolucent;
B. Type 2: predominantly echolucent;
C. Type 3 (predominantly echogenic);
D. Type 4: uniformly echogenic and
E. Type 5: unclassified plaques *(from our ultrasound unit).*

Plaque texture

Plaque texture is defined either as homogeneous or heterogeneous. It reflects the distribution of the grey-scale levels in a given area of the plaque (spatial variation of the grey tone). The term homogeneous is applied to plaques exhibiting a uniform consistency irrespective of their echogenicity. The term heterogeneous is used for plaques of non-uniform consistency having both hypoechogenic and hyperechogenic areas. Homogeneous plaques have a uniform texture and present a smooth and regular surface, whereas heterogeneous plaques may have either a smooth or an irregular surface [16].

Plaque surface

The surface is defined as smooth and regular, mildly irregular in the case of height variations of between 0.4 and 2 mm on the contour of the plaque, or ulcerated. Ultrasonographically an ulceration corresponds to an irregularity or break in the surface of the plaque which must be visualised on 2 different planes. Ulcerations must meet 3 criteria: the recess must be at least 2 mm deep and 2 mm long, have a well defined wall at its base and exhibit an area of reversed flow (without frequency aliasing) within the recess or a zone of low flow signal at the level of the recess (fig. 2). The luminal margins are better delineated by colour Doppler flow imaging (CDFI) or by power Doppler imaging (PDI). These two techniques significantly improve delineation of the margin of the plaques, in particular when an- or hypoechogenic plaques are evaluated (fig. 3)

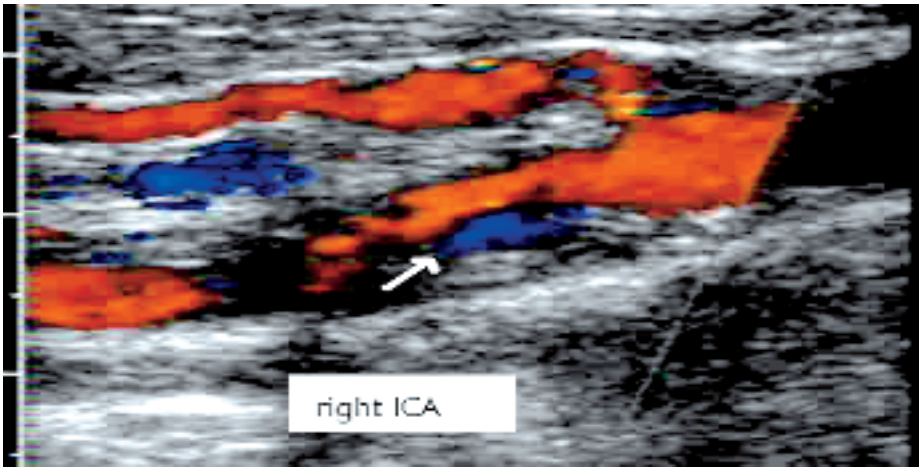


Figure 2

Ulcerated plaque of the internal carotid artery in a 64-year-old symptomatic patient. Notice the reversed flow on the surface of the plaque (white arrow) *(from our ultrasound unit).*

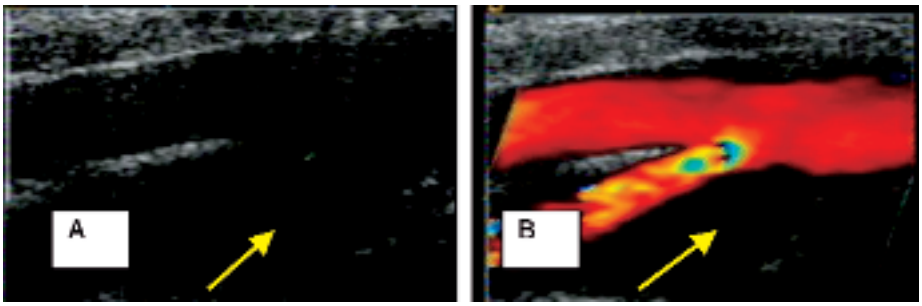


Figure 3

A. Anechogenic plaque of the internal carotid artery (yellow arrow) seen on B-mode.
B. Color Doppler flow imaging allows a better identification and delineation of the plaque *(from our ultrasound unit).*

Morphological ultrasound characteristics and risk of stroke: echogenicity, plaque texture and surface

The first prospective study on the natural history of asymptomatic carotid plaques in relation to the development of TIAs or stroke was reported by Johnson and coworkers in 1985 [17]. At the end of the 3-year follow-up, the incidence of TIAs and stroke was twice as high in the group of patients with soft plaques and more than 75% stenosis as in that with dense plaques with the same degree of stenosis. This was the first study to indicate that the ultrasonic character of the plaque was associ-

ated with a higher risk of developing stroke. Similarly, Langsfeld et al. studied 419 patients with asymptomatic plaques for 15–22 months and found anechogenic plaques to be at increased risk of becoming symptomatic compared with dense and echorich plaques ($p < 0.02$) [23]. In another study, O'Holleran et al. followed up 293 patients for an average of 46 months and showed that 100% of the patients with a soft lesion involving >75% stenosis became symptomatic as compared with only 60% of those with a dense plaque ($p > 0.05$) [24]. Similar results were reported by Bock et al., who showed that echolucent plaques were associated with a 5.7% incidence of TIAs whereas echogenic plaques only generated a rate of 2.4% ($p < 0.0001$) [25]. In the Tromso study a total of 223 subjects with carotid stenosis (123 with 35%–49% and 100 with 50%–99% stenosis) and 215 control subjects matched by age and sex were followed up for 3 years [10]. The objective of the study was to determine whether plaque morphology was associated with an increased risk of ischaemic stroke and/or other cerebrovascular events. Plaque echogenicity was assessed by ultrasound at baseline and scored as echolucent, predominantly echolucent, predominantly echogenic, or echogenic. The results of the study showed that subjects with echolucent plaques had an increased risk of ischemic cerebrovascular events independently of the degree of stenosis and other cardiovascular risk factors, and that subjects at high risk of ischaemic vascular events may be identified by ultrasound assessment of plaque morphology. However, many clinical ischaemic events occurred in this study in a vascular territory which was different from that supplied by the artery with the echolucent plaque. It was therefore suggested that plaque echolucency acted more like a marker of a higher risk of stroke than as a direct cause of the cerebrovascular event. It must also be emphasised that most of the abovementioned studies culminated in strokes and TIAs as end-point criteria; hence more studies with large cohorts and taking only stroke as an endpoint are still needed to confirm this potential embolic role of echolucent plaques.

In follow-up of a group of both symptomatic and asymptomatic patients, Sterpetti and colleagues found new neurological events occurring in 19 out of 71 carotid arteries (27%) with heterogeneous plaques, whereas new events were only seen in 6 carotid arteries out of 167 (4%) with homogeneous plaques ($p < 0.001$) [26]. Similarly, AbuRahma et al. recently reported a 2-year follow-up study of 382 asymptomatic patients with 60%–69% stenosis and likewise showed that heterogeneous plaques were significantly associated with an increased risk of stroke or TIA in comparison with homogeneous plaques [27]. The authors suggested that prophylactic endarterectomy for 60%–69% asymptomatic stenosis may be justified if associated with a heterogeneous pattern. Fitzgerald and O'Farrel also found a heterogeneous structure and irregular surface to be associated with the development of subsequent events [28].

Carotid plaque surface irregularity or ulceration are believed to play an important role in ischaemic stroke risk. Indeed, these alterations of plaque surface may expose thrombogenic layers of the plaque such as the necrotic core, with the possibility of a subsequent thrombus adhering to the plaque which further leads to embolisation. So far the only significant data in the literature on this topic concern the role of ulcers assessed by angiography in symptomatic tight carotid stenosis. In a review of patients enrolled in the North American Carotid Endarterectomy Trial, Eliasziw et al. found a higher risk of subsequent stroke if angiographic evidence of a plaque ulcer was demonstrated [29]. In unoperated patients with non-ulcerated 85% carotid stenosis, the risk of ipsilateral stroke at 24 months was 21.3% compared with 43.9% in patients with ulcerated 85% stenosis. In patients with 95% carotid stenosis the 2-year risk of ipsilateral stroke was 21.3% in patients without evidence of ulcer and 73.2% in patients with ulcerated lesions ($p = 0.005$). Similarly, Streifer et al. demonstrated in the NASCET trial that in patients on medical treatment with severe stenosis, angiographically irregular plaques were associated with a higher risk of stroke in comparison with patients presenting plaques with a smooth surface. This was also analysed in the ECST trial, which showed that stroke risk was increased among patients with irregular plaques for all degrees of stenosis, and that the association was also independent of other clinical and angiographical factors [30]. Despite the evidence of stroke related to plaque surface morphology, only a few ultrasonographic studies have addressed this particular question. In 1992, Steinke et al. reported 63 patients with 80% or greater stenosis and showed that ulcerated plaques in ultrasound were more frequently found among symptomatic (43%) than asymptomatic patients (23%) [14]. With the use of B-mode ultrasound, the sensitivity for identification of ulceration is 77% in plaques with 50% stenosis or less, but only 41% in plaques of >50% stenosis ($p = 0.03$). For angiography the sensitivity is similar (77% and 48% respectively). This lack of correlation may be due to the different time intervals from the onset of symptoms, ultrasound investigations and surgery: Lusby et al. reported a re-endothelialisation process and suggested that ulcers may heal after the neurological events and so cannot be found on ultrasound when performed some time after the occurrence of symptoms [31].

Ultrasound studies with visual analysis and histological plaque composition

Table 1 shows the most important studies conducted so far on the correlation between ultrasound-evaluated plaque morphology and the corresponding histological findings. The majority of these studies demonstrated that anechogenic plaques represent either necrotic or haemorrhagic lesions and that the echogenic appearance in ultrasound predicts rather a predominantly fibrotic tissue. This is in particular the case when the plaque is homogeneously echogenic. As mentioned above, heterogeneous plaques are related in several studies to haemorrhagic content; however, more recent studies based on a quantitative or semiquantitative approach also relate the presence of lipid necrosis to this heterogeneous pattern. Small calcifications are chiefly found in heterogeneous echogenic plaques.

Table 1

Correlation between plaque morphology on ultrasound and histological composition (based on visual analysis).

Author	Year	n	Anechogenic	Echogenic	Homogeneous	Heterogeneous
Reilly LM [16]	1983	54	Haemorrhage Lipids	Calcification	Fibrous tissue	Haemorrhage
O'Donnell TF [32]	1985	54	Lipids Haemorrhage	Fibrous tissue Calcifications	Fibrous tissue	Haemorrhage
Bluth EI [33]	1986	50	Haemorrhage	Fibrous tissue	Fibrous tissue	Intraplaque haemorrhage
Ratliff DA [34]	1985	39	No correlation	Calcifications	No correlation	No correlation
Aldoori MI [35]	1987	27	Haemorrhage	Fibrous tissue	Fibrous tissue	Haemorrhage
AbuRahma AF [36]	1998	135	–	–	–	Haemorrhage
Gray-Weale AC [37]	1988	220	Haemorrhage	Fibrous tissue	Fibrous tissue	Haemorrhage
Spagnoli LG [38]	1988	43	Haemorrhage Lipids	Fibrous tissue Calcifications	Fibrous tissue	NI
Widder B [19]	1989	169	Haemorrhage Lipids	Fibrous tissue	Fibrous tissue	NI
Feeley TM [39]	1991	52	Haemorrhage Lipids	Fibrous tissue	Fibrous tissue	NI
ECPSP* [12]	1995	270	Haemorrhage Lipids	Fibrous tissue Calcification	NI	Calcifications
Droste DW [40]	1997	29	Haemorrhage Thrombosis Fibrous tissue	Hemorrhage	Hemorrhage Thrombosis Fibrous tissue	Haemorrhage Thrombosis
Gronholdt MLM [41]	1997	78	Lipids	Fibrous tissue Calcifications	NI	Calcifications
Schulte-Altedorneburg [42]	2000	44	Lipids Haemorrhage Thrombosis	Fibrous tissue	Lipids Haemorrhage	Lipids Calcifications
Lammie [43]	2000	42	Necrosis (patchy)/ Haemorrhage (round)	NI	NI	Necrosis/haemorrhage

NI: no information

Reproducibility studies of plaque morphology characterisation

A highly variable rate of inter- and intraoperator agreement has been documented with the visual systems of plaque characterisation. The three-type classification system (Type 1 hypoechoic, Type 2 isoechoic and Type 3 hyperechoic) proposed by Polak and coworkers [44] showed excellent interoperator reproducibility attaining a κ value of 0.95, while Arnold and colleagues, using a four-type classification system for echogenicity (Gray-Weale: Type 1, hypoechoic plaques and Type 4, hyperechoic plaques), reported κ values as low as 0.52 [44]. A κ value of 0.79 was further observed by Geroulakos et al. with the five-type classification system [20]. There may be several reasons for such variability. Classification systems with two or three categories are obviously simpler and their reproducibility may therefore be easier to obtain. This is demonstrated in several studies showing improvement of the κ values by reducing the number of classification systems [44, 45]. However, it should be noted that the echostructure of the plaque (homogeneous or heterogeneous pattern) may count for less in a two or a three-type classification and an additional approach may therefore be needed. Since the echostructure of the plaque is of prognostic value it is important to consider a classification system which allows simultaneous evaluation of plaque echogenicity and heterogeneity. In the five-type system the plaques belonging to categories 2 or 3 present a heterogeneous pattern, either with predominant echolucent areas (Type 2) or with predominant echogenic

zones (Type 3), whereas those belonging to categories 1 or 4 present a homogeneous pattern. Further, the presence or absence of different reference structures used in these classification systems may also be responsible for their wide variability. For instance, de Bray et al. reported interobserver agreement of the overall echogenicity of κ 0.31; for anechogenic plaques with a predetermined reference structure (blood vessel lumen), the κ value increased to 0.47. This variability suggests that the reference structure used for echogenic and hyperechogenic plaques (intima-media thickness) may have been insufficient [46]. On the other hand, in the Tromso study, based on the Gray-Weale four-type classification system, two reference structures were used, viz. the bloodvessel lumen for echolucency (Type 1) and the bright far wall media-adventitia interface for hyperechogenicity (Type 4); a very good between- and within-sonographer agreement was achieved with κ values of 0.72 and 0.76 [22] respectively. Overall, the highly variable rate of reproducibility corresponds to the number of items and observers, and also reflects the lack of a standardised method.

Regarding surface analysis, Sitzer and coworkers analysed 43 plaques (30 symptomatic and 13 asymptomatic). With ultrasound analysis they only found 28% ulcerated plaques, whereas histology indicated 46%. These results suggest a sensitivity of 0.33, a specificity of 0.76, a negative predictive value of 0.54 and a positive predictive value of 0.57. The interobserver value was κ 0.57 [47].

Recent developments

In real-time compound imaging the ultrasound beam provides multiple transmit angles in the course of a single scan. Thus, the averaging process improves the signal-to-noise ratio for the target location, enhances ultrasound visualisation of plaques in B mode and enhances intra- and interobserver agreement. Kern and colleagues recently demonstrated that this new approach allowed better characterisation of plaque echogenicity and surface, thereby improving the interobserver κ values, reaching 0.83 for echogenicity and 0.72 for surface [48]. Besides ultrasound, other imaging techniques for showing plaque morphology and surface structure have also been developed more recently. Computed tomography (CT) is capable of showing the calcium content and specific site of the plaques. However, lipid content and fibrous tissue cannot be deduced reliably. Further, the currently available image resolutions limit detailed imaging of surface characteristics. Magnetic resonance imaging (MRI) makes it possible to recognise in vivo both the fibrous cap and necrotic core as well as intraplaque haemorrhage [49–51].

Computerised evaluation of plaque echogenicity: grey-scale median (GSM)

The operator-dependent and subjective method of visual plaque characterisation has been a major concern in recent years. A new method has therefore been developed using computer-aided analysis providing a more quantitative, more objective and more operator-independent assessment of plaque echostructure [52]. The analyses are performed on B-mode images transferred from the ultrasound machine to a personal computer. The software is by Adobe Photoshop program (fig. 4). After identifying the luminal plaque margins using the colour images as a guide, an automatic switch-off of the colour is performed. The grey-scale median (GSM) of the frequency distribution of grey values of the pixels within the plaque are used as the measure of echogenicity. Because

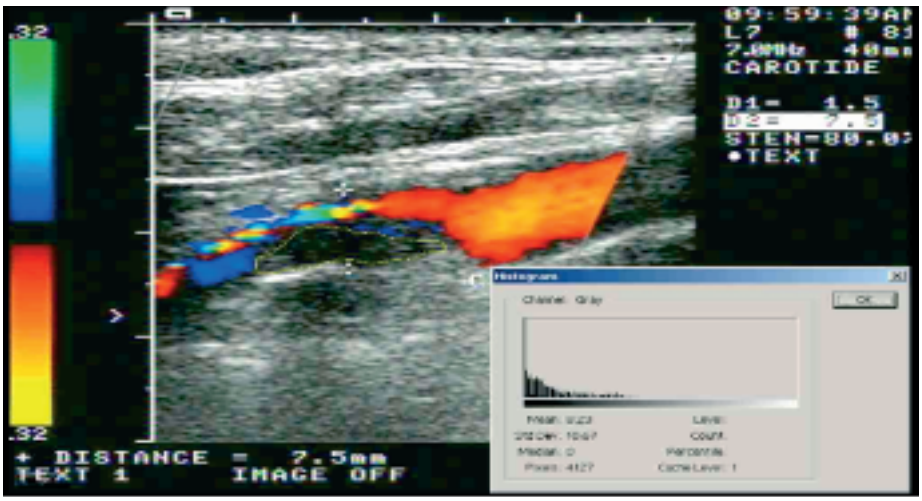


Figure 4

Anechogenic plaque with a low GSM value of 8. Notice also the low value of the standard deviation (10.6) corresponding to a homogeneous plaque pattern *(from our ultrasound unit).*

of the different instrument settings used, comparisons of the GSM values between different centres were initially difficult. A method was therefore developed of normalising images using digital image processing and 2 references (blood and adventitia). The carotid plaques are first normalised by a linear scaling method provided by the software in order to obtain, as references, a GSM value in the range of 0–5 for the vessel lumen and a GSM value in the range of 185–195 for the adventitia. Normalisation of the plaque then allows optimal inter- and intraobserver agreement. After this normalisation the plaque is outlined and its overall brightness evaluated by means of GSM (grey-scale range: 0–255; black = 0, white = 255) [52]. El-Barghouty et al. analysed 87 patients with >50% stenosis and found that plaques with a GSM value of less than 32 were associated with an incidence of 55% cerebral infarction, whereas plaques with a GSM value of more than 32 exhibited an incidence of only 11% ($p < 0.001$, RR 22 95% CI 4.7–108) [52]. Similar results were also obtained by Biasi and colleagues, who reported a stroke incidence of 40% if the GSM value of the plaque was less than 50, and of only 9% if the GSM value was above 50 ($p < 0.001$) [53]. Furthermore, in a recent prospective study with a follow-up of 4.4 years and including 111 asymptomatic and 135 symptomatic patients with >50% stenosis, Gronholdt et al. also demonstrated that anechogenic (echolucent) plaques as determined by B-mode ultrasound with computer-assisted imaging predicted future strokes [54]. In symptomatic patients the relative risk of ipsilateral ischaemic stroke for anechogenic versus echogenic plaques was 3.1% (95%CI, 1.3 to 7.3), whereas for 80%–99% versus 50%–79% stenosis the relative risk was 1.4 % (95% CI, 0.7–3.0). These findings led to the conclusion that anechogenic plaques causing >50% diameter stenosis were associated with an increased risk of future stroke in previously symptomatic patients. Measurement of plaque echogenicity should therefore improve selection of patients for endarterectomy. However, although characterisation of the plaque's internal structure assessed by computer-assisted imaging correlates closely with clinical symptoms, as demonstrated in the above-mentioned studies, conflicting results have been obtained regarding histological studies. Table 2 summarises the different histological studies performed with respect to GSM analysis of the plaque. GSM analysis represents a median value of the whole atherosclerotic area and therefore may not necessarily reflect the presence of particular regional components. It has recently been demonstrated that a stratified GSM assessment, analysing each millimetre from the surface to the bottom of the plaque combined with colour mapping could predict plaque histology better than the usual overall GSM measurement. A profile of the regional GSM as a function of distance from the plaque surface could be generated (fig. 5). Plaque pixels were further mapped into 3 different colours depending on their GSM value. A necrotic core located in a juxtaluminal position was associated with significantly lower GSM values ($p = 0.009$) and with a predominant red colour (GSM <50) at the surface ($p = 0.0019$). With respect to the thickness of the fibrous cap and the position of the necrotic core, the sensitivity and specificity of the predominant red colour of the whole plaque was 45% and 67%, 53% and 75% respectively; considering the predominant red colour of the surface, the sensitivity and specificity increased to 73% and 67%, 84% and 75% respectively. The stratified GSM measurement combined with colour mapping correlated well with the various histopathological components and also made it possible to identify determinants of plaque instability [60] with a high degree of accuracy.

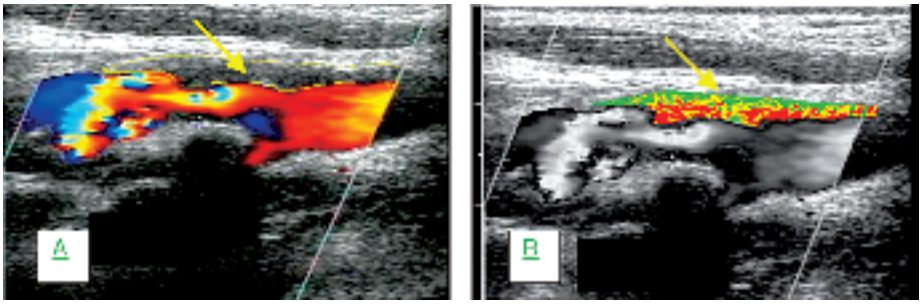
Table 2

Correlation between computerised analysis (GSM) of carotid plaque and histopathological analysis.

Authors Year	Number plaques	Fibrous	Necrotic core	Haemorrhage	Calcified	Surface
El-Barghouty NM [55], 1996	52	High GSM p <0.001	Low GSM p <0.05	Low GSM p <0.05	NI	NI
Matsagas MI [56], 2000	54	NS	NS	NS	High GSM (>35) p <0.02	NI
Tegos TJ [57], 2000	71	NS	NS	Low GSM p = 0.04	NS	NI
Gronholdt ML [58], 2002	106	high GSM, low macrophage %	Low GSM, high macrophage %	Low GSM, high macrophage %	High GSM, high macrophage %	NI
Denzel C [59], 2003	107	NI	NS (soft plaques)	NI	NS (hard plaques)	NS

Figure 5

A. The plaque is delineated by colour Doppler flow imaging at its surface and by adventitia at the bottom (yellow arrow).
B. Colour Doppler flow imaging is switched off. Colour mapping of the plaque (yellow arrow). shows the following proportions for the whole plaque: red 38% (GSM <50), yellow 24% (GSM >50 and <70) and green 6.7% (GSM >70); for the surface of the plaque the colours are distributed as follows: red 68%, yellow 38% and green 27%.



Conclusions

Plaque morphology plays an important role in the pathogenesis of symptomatic carotid disease. The aim of ultrasound investigation is to obtain a well standardised method which is able to determine an unstable plaque and its particular features, namely the presence of ulcers, a hypogenic lesion, a thin fibrous cap and a necrotic core located near the surface. So far, high resolution ultrasound has allowed assessment of the morphological characteristics associated with an increased risk of subsequent stroke, such as anechogenic and and heterogeneous plaques or plaques presenting an ulcerated surface. However, this evaluation is based on a visual analysis using different classification systems and presents high intra- and interobserver variability. Computer-assisted analysis of plaque echogenicity represents a more objective and quantitative method than visual analysis alone, shows a very close correlation between low GSM values, corresponding to anechogenic plaques, and the presence of symptoms. However, GSM analysis represents the median value of the echogenicity of the whole plaque and may not take into account regional differences within the same plaque and in particular with regard to its surface. Stratified GSM analysis, determining the GSM in each one millimeter-thick stratum of the plaque, may therefore represent an additional method of determining different components of the plaque and in particular determinants of plaque instability such as thinning of the fibrous cap and the position of the necrotic core near the surface. Further trials with clinical endpoints and with reproducibility analysis are needed to validate this method.

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