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REVIEW ARTICLE

Carotid Plaque Morphology: A Review

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The recent North American Symptomatic Carotid Endarterectomy Trial has answered fairly conclusively the questions concerning the optimal management of patients with symptoms who have a >70% stenosis of the internal carotid artery. It has also had the effect of refocusing attention on carotid pathology. The main question still to be answered is whether surgical management is the optimum treatment for other groups of patients with carotid disease. From various studies done on the natural history of carotid plaques it is apparent that there are subgroups who may benefit from surgery, namely those who will progress to stroke if not treated. The problem comes in identifying these subgroups by the factors which cause them to progress. This paper aims to review the role that plaque morphology has in the development of symptoms and whether it should be included with degree of stenosis in assessing the risk of a carotid plaque. The non-invasive assessment of plaque morphology is also reviewed. The evidence from this review does not support the use of plaque morphology as a discriminating factor for carotid endarterectomy at present.

Introduction

Recent trials[1,2] have shown quite conclusively that carotid endarterectomy is the treatment of choice in symptomatic patients with a >70% stenosis of the internal carotid artery. However there is still doubt as to whether an operation is the best treatment for other groups, namely those patients with symptoms but lower grade lesions (50–75%) and those patients who are as yet asymptomatic despite having a high grade stenosis. The results of clinical trials in progress may shed further light on the indications for carotid endarterectomy.

Some earlier studies found that patients who have asymptomatic stenoses are at an increased risk of developing symptoms.[3,4] Hertzer *et al.*[3] found that 22% of patients with asymptomatic stenoses went on to have a transient ischaemic attack or stroke within 5 years and they also identified subgroups of patients who had either a >70% unilateral stenosis, or bilateral stenoses >50% to be more at risk (33 and 36% respectively). Similar results were found by Moore *et al.*[4] with a 16% overall stroke rate over 5 years, increasing to 21% in patients who had a >50% stenosis. Fourteen percent of those who were initially found to have a <50% stenosis also became symptomatic, but the degree of stenosis was not reassessed during the follow-up period and the degree of progression to over 50% is not known. Disease progression has been demonstrated to play a factor in producing symptoms. In one study[5] it was found that during the follow-up of patients with asymptomatic plaques, 89% who became symptomatic had a disease progression of greater than 80% and that these lesions carried a risk of stroke or TIA of 46% within 12 months. These studies concentrated merely on the degree of stenosis and it is now widely accepted that other factors could be implicated in indicating risk.

To evaluate the importance of carotid plaque morphology, a review of the literature has been performed with the aid of a Medline search.

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Plaque Composition

The carotid bifurcation is particularly prone to the development of atherosclerotic plaques and this has been attributed to the disturbances in flow found at the bifurcation.[6] It has been demonstrated that carotid plaque formation is greatest at points at which flow separation and low shear stresses are present.[7,8] Two

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major types of atherosclerotic lesions are found, simple fibrous plaques and complicated lesions. The simple fibrous plaque appears whitish and generally consists of a central core of lipid (principally cholesterol) and cell debris, surrounded by smooth muscle cells, collagen and elastic fibres. A fibrous cap of varying thickness separates the lipid core from the lumen.[6] A fibrous plaque can degenerate to form a complicated lesion. These plaques can become calcified, haemorrhage is often found within the lesion and the surface can become irregular and frequently ulcerated.[6]

Many plaques become vascularised,[9] with small thin walled vessels thought to be derived from the vasa vasorum and from the lumen. These vessels are very fragile, can easily rupture and are thought to be a source of intraplaque haemorrhage.

There are two ways in which a carotid artery plaque can produce a stroke. Firstly by hypoperfusion which will only occur in the presence of high grade stenoses and is the reason why degree of stenosis has always played such a dominant role in patient selection. Secondly by embolism which does not necessarily require a high grade stenosis. It has been found that the complicated lesions commonly give rise to symptoms and these plaques are more likely to produce embolic episodes.[10, 11]

Two main factors have been commonly identified as elements which may increase the risk of stroke along with degree of stenosis, the presence of intraplaque haemorrhage and the presence of ulceration.

The Importance of Intraplaque Haemorrhage

Intraplaque haemorrhage (IPH) was noted early on as a characteristic of carotid artery plaques and much emphasis has been placed on its role in plaque development and its relation to symptoms. It has been attributed to three sources: rupture of vessels derived from the vasa vasorum in the base of the lesion; rupture of superficial vessels (possibly derived from the lumen); and dissection of blood from the arterial lumen through an ulcer or fissure.[12]

Several studies have concentrated on the incidence of IPH in carotid plaque specimens taken at endarterectomy. The overall incidence of IPH varies from 87%[13] to only 31%.[14] Some studies have found a significant correlation between the presence of IPH and symptoms[9, 14–16] whereas others have demonstrated no correlation.[17–21] Even the quantities of IPH commonly found have varied considerably between studies.[9, 17, 18, 20, 24]

Firstly, does the presence of intraplaque haemorrhage in a carotid plaque correlate with symptoms? Imparato *et al.* in their study of 376 carotid endarterectomy specimens focussed attention on the role of intraplaque haemorrhage in plaque progression.[14] In a gross, macroscopic examination of the histological characteristics of the plaques, he found that the presence of intraplaque haemorrhage was the only factor significantly more common in plaques from symptomatic patients than those from asymptomatic patients. When degree of stenosis was also taken into account, the difference only appears significant in stenoses of > 70%, with 43% of the symptomatic plaques having IPH compared to only 22% of the plaques from asymptomatic patients. These results were largely supported by the work of Lusby *et al.*[16] and Persson *et al.*[15] who both showed significant correlation between intraplaque haemorrhage and symptoms. Lusby *et al.*[16] found that in patients with a >50% stenosis, 39/46 (85%) plaques from symptomatic patients had intraplaque haemorrhage, compared to only 7/20 (35%) plaques from asymptomatic patients. They also classified the age of haemorrhage based upon its appearance with an elastochrome stain and the presence or absence of an inflammatory response. Furthermore they defined acute, recent and remote haemorrhage as being up to 1 week, up to 6 weeks and greater than 6 weeks old respectively. There was a very good correlation between age of haemorrhage and the onset of symptoms with 12/16 patients who had their operation within 1 week of symptoms having acute haemorrhage and 26/36 patients with symptoms that occurred between 1 and 6 weeks of the operation having recent haemorrhage.

Persson *et al.*[15] studied 57 plaques from endarterectomy specimens, 55 of which had a >60% stenosis. Thirty-three out of the 34 plaques from symptomatic patients had IPH and only 11 out of the 21 plaques from asymptomatic patients. A study by Ammar *et al.*[13] however found that 42/44 (95%) of symptomatic plaques had IPH, 16/19 (84%) plaques with non-focal symptoms and 25/32 (78%) symptomatic plaques. A significant difference was only found between symptomatic and asymptomatic plaques when repeat haemorrhages were taken into account. 29/44 symptomatic plaques had multiple haemorrhages compared to only 12/32 asymptomatic plaques. However, little information is given on degree of stenosis in this study and it is possible that a higher incidence of high grade stenoses in the asymptomatic plaques may have skewed the results.

These studies all tend to support a hypothesis put forward by Persson *et al.*[15] that IPH is the cause of plaque progression. They believe that rupture of small

vessels within the plaque can cause the plaque to suddenly enlarge. This leads to symptoms either by the sudden increase in degree of stenosis causing hypoperfusion or by erosion of the plaque with the resultant eruption into the lumen causing embolisation. This hypothesis is supported by the results of Fryer *et al.*[9] who found close association between the small vessels in the plaque and IPH with new vessels seen in 52 out of the 67 plaques that had recent haemorrhage, and in 40 of these cases the vessels were closely associated with the haemorrhage.

However recent reports have put doubt on these earlier findings. Bassiomy *et al.*'s study[16] of 45 plaques with high grade stenoses removed at endarterectomy and 17 non-stenotic plaques from autopsy specimens found no significant difference in the incidence of IPH between the stenotic symptomatic and asymptomatic groups (68 and 86% respectively). There was however a significant difference in the incidence of IPH between the stenotic and non stenotic plaques. In a preliminary study of 10 plaques, Beach *et al.*[22] also finds a correlation between degree of stenosis and the incidence of intraplaque haemorrhage. In a large recent study, Van Damme *et al.*[20] examined 250 carotid endarterectomy specimens, 121 from symptomatic patients and 129 from asymptomatic patients. No significant difference was found in the incidence of either recent or old intraplaque haemorrhage in the two groups. Von Maravic *et al.*[21] also found a lack of association between intraplaque haemorrhage and symptoms.

Recent studies have recognised that the quantity of IPH may be an important factor. Bassioumy *et al.*[17] found the quantity of IPH much smaller than previously reported with IPH (recent and remote) only occupying 2.5% of the plaque area in the symptomatic plaques. These results are also supported by the work of Leen[18] in which 40/59 (68%) of plaques had IPH but occupying greater than 1% of the area in only 21 plaques. In only one plaque did IPH constitute more than 15% of the plaque. This is at variance with the study by Fryer *et al.*[9] which reports recent haemorrhage as occupying greater than 50% of the plaque area in 47% of cases. Imparato *et al.*[23] also defines significant haemorrhage as occupying greater than 50% of the plaque area. Van Damme *et al.* found that small, recent intraplaque haemorrhage was a very common finding in all plaques, but voluminous IPH, defined as occupying at least half of the plaque area, was found in only 96 of the 168 plaques containing IPH and suggests that the volume must be taken into account in assessing the importance of IPH.

Leen *et al.*[18] and Feeley *et al.*[19] identify an homogeneous pink granular material mixed with varying quantities of cholesterol. They suggest that this is the "remote haemorrhage" defined by Lusby *et al.*[16] but state that no blood breakdown products could be identified within it and that although the origin and nature of this material is unknown there is no evidence that it is old or degenerating haemorrhage. Leen *et al.*[18] doubt the theory about plaque development put forward by Persson *et al.* and proposes an alternative hypothesis. They believe that the plaque develops by the deposition of cholesterol. Atheronecrosis develops and neo-vascularity in the plaque occurs. They believe that IPH comes from plaque breakdown allowing luminal blood to dissect into the plaque.

With this conflicting evidence it is difficult to draw conclusions on the role of intraplaque haemorrhage in producing symptoms. Obviously the origin and nature of the amorphous material identified by Leen *et al.*[18] and Feeley *et al.*[19] must be investigated further as if it proves not to be an end result of IPH, there will be little evidence to support the role of IPH in plaque development. However this does not account for the huge differences in quantities of recent haemorrhage found in different studies and this must be investigated further. The degree of stenosis is an important consideration in assessing carotid plaques and some studies have shown that intraplaque haemorrhage is more common in plaques causing a high grade stenosis. It is therefore important that the symptomatic and asymptomatic groups in a study should be matched for degree of stenosis. As most centres only operate on asymptomatic plaques in the presence of high grade lesions, the asymptomatic groups often include more high grade lesions than the asymptomatic groups and this could affect the results.

The Importance of Ulceration in Carotid Plaques

Ulceration has been noted as a feature of plaques removed at carotid endarterectomy and many studies have been done to see whether ulceration makes a plaque symptomatic. Ulceration has been defined as an observable disruption of the intima, exposing adjacent atheromatous plaque or media.

Ulceration is believed to be important because it causes exposure of the thrombogenic layers of the plaque and subsequent thrombus adhering to the plaque can break off to produce emboli. Imparato *et al.*[14] in a study of the gross morphology of carotid plaque found no significant difference between the number of symptomatic plaques with ulcerations compared to asymptomatic plaques (48% symptomatic plaques and 41% asymptomatic plaques had

ulcerations). He also found no correlation between the degree of stenosis and the occurrence of ulcers. Bassioumy *et al.*,[17] comparing high grade symptomatic plaques with high grade asymptomatic plaques, partly agreed, finding no significant difference in the occurrence of ulcers between the groups (58 and 43% respectively). However he did find ulceration in 24/25 (96%) plaques that were present with a >75% stenosis compared to only 1/17 (6%) causing <50% stenosis. Comerota *et al.*[24] found an incidence of 68% of symptomatic plaques having ulceration compared to 51% of asymptomatic plaques.

In contradiction Fryer *et al.*[9] found 47/71 (67%) symptomatic plaques had ulcerations compared to only 6/20 (30%) asymptomatic plaques and Sterpetti *et al.*[25] also found that ulceration was statistically related to the presence of hemispheric symptoms with 33/44 (75%) plaques with focal symptoms, 6/22 (27%) with non-lateralising symptoms and 6/67 (8%) asymptomatic plaques having ulcerations. Van Damme *et al.* found ulceration in 46/121 (38%) of symptomatic plaques, significantly higher than in asymptomatic plaques (23/129). Eliasziw *et al.*,[26] in a study of 659 symptomatic patients with high grade stenoses from the NASCET Trial, found arteriographic evidence of ulceration in 230 plaques from the arteriograms. In the group of medically treated patients, those with arteriographic evidence of ulceration were associated with an increased risk of stroke which was also related to the degree of stenosis.

The disparity in the results can be partially explained by the fact that Fryer *et al.*[9] do not include data on the degree of stenosis at all and Sterpetti *et al.*[25] include 43 cadaver specimens with stenoses less than 60% in his asymptomatic group, whereas the symptomatic patients group had higher degrees of stenosis. If ulceration is related to degree of stenosis as is suggested, this alone would account for the difference in ulceration incidence between these two groups. Bassioumy *et al.*[17] and Comerota *et al.*,[24] who both group their patients according to degree of stenosis and symptoms, agree that in stenotic plaques the incidence of ulceration in symptomatic and asymptomatic plaques are not significantly different (58 and 43%, 63 and 49%).

Overall it would appear that there is no significant correlation between the presence of ulceration and symptoms.

Non-invasive Investigations for Plaque Characteristics

There is still much work to be done before the pathogenesis of carotid artery plaques is completely understood. However if a factor can be identified which relates well to the risk of developing a stroke, it will only be useful if it can be detected preoperatively. Two major methods are currently used as standard diagnostic tests for carotid disease, angiography which is considered the "gold standard" for diagnosis and carotid Duplex ultrasound. Duplex ultrasound has been found to agree well with arteriography in calculating the severity of a lesion[27] and has the advantage that it can provide some information on plaque composition. Also its non-invasive nature makes it ideal for serial investigations.

Degree of stenosis has been the main criterium for selecting patients for carotid endarterectomy, along with symptoms. However there is great variability in the methods used to determine degree of stenosis. Many centres now use Duplex ultrasound, but different classifications are used in different centres. Both the NASCET trial[1] and the ECST[2] trial used arteriography but whereas NASCET used the ICA diameter distal to the stenosis as a reference point, ECST used the bulb diameter. As Strandness[28] points out in his review of these trials, this would result in the same stenosis being graded as 0% in the NASCET trial and 50% in the ECST trial. Clearly this lack of uniformity could result in differences between studies and in the future fixed, widely accepted guidelines for classifying stenoses would be useful to ensure comparability between centres.

Although recently some doubt has been placed on the role of intraplaque haemorrhage in producing symptoms, it has still been shown that "soft", lipid high plaques are more likely to cause symptoms than the "hard" mainly fibrous plaques. Several studies have been performed to see if an ultrasound investigation can pick out the difference between these types of lesions.[19, 29, 30] Generally the plaques have been classified into four groups, based on the echogenicity of the ultrasound image.[29] Group I plaques are predominately echoluscent, sometimes with a thin cap noted. Group II plaques are mainly echoluscent but with some echogenic areas. Group III plaques are mainly echogenic but with some echoluscent areas and Group IV plaques are uniformly echogenic. Some centres have included a fifth group to allow for plaques that were poorly visualised and could not be classified correctly. Other centres have based their carotid plaque classification according to the homogeneous or heterogeneous characteristics of the ultrasound image.[31]

Several studies have compared the ultrasound appearance of asymptomatic plaques to symptomatic plaques. Leahy *et al.*[32] in his study of 65 symptomatic

and 151 asymptomatic stenoses, with no difference in the degree of stenosis between the two groups, found that 50% of the heterogeneous plaques were associated with symptoms compared to only 25% of the homogeneous plaques. Giannona *et al.*[33] studied 75 patients who had undergone carotid endarterectomy and had an asymptomatic, 15–45% stenosis in the contralateral carotid artery. Twenty-nine were homogeneous with only five developing symptoms during the follow-up period. Forty-six were heterogeneous and 20 of these developed symptoms, significantly higher than in the homogeneous group.

Langsfeld *et al.*[34] classified groups of symptomatic and asymptomatic plaques according to their echogenic properties.[29] He found that 69% of symptomatic plaques were type I or II lesions, whereas 67% of the contralateral asymptomatic vessels had type III or IV lesions. In the follow up series it was found that the more echoluscent plaques (types I and II) were more likely to become symptomatic (15/98 compared to 25/338 type III and IV plaques). Similarly Geraloukas *et al.*[35] using the same groups for classification found 57/70 symptomatic high grade stenoses to have type I or II lesions and 43/73 of asymptomatic plaques with high grade stenoses to be type III or IV plaques.

A few studies have correlated the preoperative ultrasound appearance of the plaque with the histological findings. Wolverson *et al.*[30] did *in vitro* studies of autopsy and carotid endarterectomy specimens to correlate the ultrasound appearance with the actual histology. He showed that lipid rich regions were least echogenic and calcified areas the most echogenic. Collagen was very echogenic but did not produce the acoustic shadowing associated with calcification. Minor surface irregularities seen on ultrasound did not indicate ulceration; there needed to be a localised or abrupt interruption of the intimal surface. Gray-Weale *et al.*[29] in a study of 244 carotid endarterectomy specimens found type I or II plaques associated with 132/166 (80%) of plaques with the macroscopic appearance of IPH. Type III or IV plaques occurred primarily in the plaques found to be simple fibrous plaques at operation. Feeley *et al.*[19] using the same plaque classification as Gray-Weale *et al.* found that Duplex scanning had a sensitivity of 94% and a specificity of 67% in determining hard from soft plaques. Duplex ultrasound scanning has also been used to assess plaques for ulceration but with variable results. Rubin *et al.*[36] in his study of 32 carotid endarterectomy plaques found that the Duplex scan had picked up 13/14 ulcers found whereas angiography had detected only five. Twenty-three plaques were found to have surface irregularity and 20 of these were correctly classified by ultrasound. However Comerota *et al.*[24] in their study of 126 carotid endarterectomy plaques found the accuracy of detecting ulcers varied with degree of stenosis. He obtained the highest sensitivities in stenoses < 50%, correctly identifying 10/13 ulcerations. The worst stenosis group was > 90% where only 8/20 ulcerations were identified with Duplex scanning.

Giannoni *et al.*[33] classified plaques into smooth or irregular and found that of the 25 plaques with a smooth surface only three went on to develop symptoms whereas of the 50 plaques with an irregular surface, of which 16 were counted as ulcerated, 14 developed symptoms. Widder *et al.*[37] however found that although ultrasound classified 58/62 non-ulcerated plaques correctly, ultrasound appearance of an irregular plaque surface revealed relevant ulceration at surgery in only 12/45 cases. Also in 58/165 cases the plaque was not visualised adequately for classification.

This illustrates the variability found in detecting ulceration by B mode ultrasonography. Good accuracy is very dependent on image quality and the experience of the ultrasonographer in deciding whether an irregular surface is ulcerated or not. A more recent study[38] has looked into the role of colour Doppler in detecting carotid plaque ulcerations. The authors used solely the detection of vortices in the flow to diagnose an ulceration; 41/43 ulcers were detected correctly with this method, with an overall accuracy of 94%. Steinke *et al.*[39] also used Doppler colour-flow imaging to study the surface characteristics of 75 plaques all causing a > 80% stenosis. Forty-three percent of symptomatic plaques were ulcerated compared to only 23% of asymptomatic plaques.

It is not clear what role mechanical factors play in plaque progression. Intimal wall thickening has been shown to be related to areas where there are low shear stresses[7,8] and perhaps the progression and disruption of the plaque is more related to these factors than just plaque composition. The advent of colour Duplex enables us to examine flow patterns around stenoses *in vivo* and it is possible that detailed examination of these may reveal differences between symptomatic and asymptomatic plaques. Also Woodcock[40] points out that many plaques are noted to move within the lumen because of variations in pressure and flow during the cardiac cycle. This would set up stresses within the plaque making it more likely to disrupt the intima or the small vessels within the plaque.

Despite the uncertainty about what causes a plaque to become symptomatic, Duplex ultrasound has been shown to be able to distinguish between different plaque types and most studies agree that the symptomatic plaques tend to be less echogenic and

more heterogeneous. Presently the assessment of plaque type is very subjective. As three dimensional reconstruction techniques develop in ultrasound imaging, it should be possible to provide a more quantitative assessment of plaque morphology.[41, 42] Spagnoli *et al.*[43] have also described a densitometric approach to quantifying plaque composition which should enable more subtle changes in plaque composition to be detected ultrasonically and again allow quantification of the different plaque components.

The detection of ulceration is more difficult with a wider degree of variation. This can partially be explained by different machines producing different images. For the detection of ulcers to be sensitive and accurate, high quality images must be obtained. The advent of colour Duplex will help in the plaque classification by both showing areas of turbulence which may relate to ulcers and by better defining the borders of the plaque which can be difficult to judge.

Conclusion

There are still many important questions concerning carotid plaque morphology not answered conclusively. Randomised trials like the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial on symptomatic disease and the current asymptomatic carotid endarterectomy trial will help to determine the optimum treatment for patients with different categories of carotid bifurcation disease defined by degree of stenosis. There is conflicting evidence on what aspects of plaque histology are related to symptoms, and neither intraplaque haemorrhage or ulceration has been consistently shown to increase the risk of stroke. However, there is general agreement that the appearance of echoluscent, heterogeneous plaques on ultrasound images do indicate a "high risk" lesion and may in the future have a role to play in selecting patients for carotid endarterectomy.

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