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Symptoms, Stenosis and Carotid Plaque Morphology. Is Plaque Morphology Relevant?

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Objectives: *To study the relationship between carotid plaque morphology and the degree of stenosis on Duplex ultrasonography and symptoms.*
Design: *Prospective open clinical study.*
Methods: *2590 patients with 5180 carotid arteries were scanned, 4560 were initially analysed in terms of symptoms but 54 were excluded, leaving a total of 4258.*
Results: *Localising symptoms were present with respect to 1342 vessels (29.4%). Two-thirds of symptomatic patients had normal carotid arteries. Tight stenosis (80–99%) was more likely to be associated with symptoms than low-grade (20–79%) stenosis ($\chi^2 = 28.0$, $p < 0.0001$). Plaque type was identified in 1558 bifurcations (36.6%). Heterogeneous type I & II plaques accounted for one third of plaques. There was a relationship between plaque morphology and degree of stenosis. At <20% stenosis only 4.4% of plaques were heterogeneous whereas at 80–99% stenosis 84.5% of plaques were heterogeneous. Amaurosis fugax was the only symptom that had any association with a particular plaque morphology. Seventy-two percent of plaques associated with this symptom were heterogeneous in nature.*
Conclusions: *Carotid plaque morphology and degree of internal carotid stenosis are mutually dependent factors and both reflect the severity of atherosclerotic disease. Plaque morphology does not add to the sensitivity of stenosis in predicting the presence of symptoms.*

Key Words: Internal Carotid Artery; Stenosis; Plaque Morphology; Stroke; Transient Ischaemic Attack.

Introduction

Carotid endarterectomy is indicated for symptomatic patients with high grade (>70%) internal carotid stenosis.[1,2] The role of surgery in the management of high-grade asymptomatic stenoses is more controversial. The benefits from prophylactic surgery in the prevention of a disabling stroke must outweigh the risks of leaving the patient untreated. Many patients with known asymptomatic extracranial carotid disease will develop transient symptoms prior to a stroke.[3–5] In these circumstances surgery is indicated at the onset of symptoms. Nevertheless, up to 7% of patients have a disabling stroke without any premonitory symptoms[5–7] and it would be advantageous if such patients could be identified in advance. The criteria for delineation of this sub-group are not clearly defined. Clearly, the degree of carotid stenosis is important[5–9] and the role of prophylactic surgery in the management of asymptomatic high grade stenosis is currently being examined in the European Asymptomatic Carotid Study.

Using Duplex ultrasonography, it is possible not only to measure the degree of carotid stenosis but also to characterise the morphology of the plaque. Despite many different methods of plaque classification, it is suggested that those plaques that can be variously described as "soft", "haemorrhagic", "echolucent" or "ulcerated" are at an increased risk of developing symptoms and therefore comprise a high-risk sub-group.[7–17] Many of the studies relating plaque morphology to symptoms are based on relatively small groups of pre-selected symptomatic patients who are undergoing surgery. In addition, the "asymptomatic" controls in these studies are usually patients undergoing prophylactic surgery or are patients with asymptomatic bruits. Asymptomatic bruits are known to be associated with a slightly increased risk of developing subsequent symptoms.[6] The conclusions from these studies may therefore not be representative of the wider atherosclerotic population. The data presented in this paper is based on a much larger series of patients undergoing carotid Duplex ultrasonography and attempts to address the relationship

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between the three variables of symptoms, plaque type and degree of stenosis.

Patients and Methods

All patients referred to the Ninewells Hospital Vascular Laboratory for carotid Duplex scanning in a 3-year period have been included. Data on symptoms, degree of stenosis, and plaque type has been routinely entered into the Ninewells Hospital Vascular Database. All Duplex scans were carried out by the same technician (JSB) who also entered all the data. Therefore uniform plaque classification, percentage stenosis and interpretation of the symptoms has been preserved throughout this period. All scans were carried out using a Toshiba FFA 270A ultrasound scanner with a 7.5MHz probe.

Plaque was classified according to the criteria outlined in Table 1. Ulcerated plaques are usually classified as type I because they are considered to contain loose clot within the ulcerated area. Plaque types I and II are classified as predominantly soft or heterogeneous and types III and IV are classified as predominantly fibrous or homogenous. Degree of stenosis in the internal carotid artery was classified according to the criteria in Table 2. In a few scans the degree of stenosis was classified as "uncertain". This usually indicated a severe stenosis or functionally occluded internal carotid artery.

Table 1. Classification of plaque types[5, 10, 12, 14]

Heterogeneous (soft, predominantly echolucent, haemorrhagic)	
Type I	Echolucent raised lesion with thin "eggshell" cap of echogenicity.
Type II	Predominantly echolucent plaque with small areas of echogenicity
Homogeneous (fibrous, predominantly echolucent)	
Type III	Predominantly echogenic plaque with small areas of echolucency
Type IV	Uniformly dense echogenic lesion

Any scans that were follow-up scans and those carried out on postoperative patients were excluded from any analysis. Data on patients with occluded arteries and those with an "uncertain" degree of stenosis were only used in the analysis of symptoms.

Each scan comprised two carotid bifurcations and all analysis is based on the hemispheric distribution of that artery. For the purpose of this study "symptomatic" disease includes only those symptoms that can be localised to the hemispheric distribution of one carotid artery. These include cerebro-vascular accident (CVA) with symptoms lasting more than 24 hours, transient ischaemic attack (TIA) with symptoms lasting less than 24 hours, amaurosis fugax (AF) and central retinal artery occlusion (CRAO). "Asymptomatic" disease includes scans that are carried out on normal carotid arteries, asymptomatic bruits (ACB), those with non-hemispheric symptoms (NON-HAEM) and vertebro-basilar insufficiency (VERBAS).

Table 2. Classification of degree of stenosis

Normal	No spectral broadening; peak systolic frequency < 3.0 kHz or velocity < 100 cm/s. No plaque on B-mode scan.
< 20% stenosis	Spectral broadening limited to diastole; peak frequency < 4.0 kHz or velocity < 125 cm/s; evidence of minor plaque on B-mode scan.
20–49% stenosis	Spectral broadening throughout waveform; peak systolic frequency ≤ 4.0 kHz or velocity ≤ 125 cm/s; obvious plaque formation on B-mode scan.
50-79% stenosis	Spectral broadening throughout the waveform; peak systolic frequency > 4.0 kHz or velocity > 125 cm/s; marked narrowing of arterial lumen on B-mode scan.
80-99% stenosis	Spectral broadening throughout the waveform; signal may be difficult to locate because of small lumen; peak systolic frequency > 6.0 kHz or velocity > 180 cm/s; peak diastolic frequency > 4.0 kHz or velocity > 140 cm/s; often difficult to visualise lumen on B-mode scan due to severe stenosis

Results

A total of 2590 patients with 5180 internal carotid arteries were examined. Of these 620 were classified as either follow-up or postoperative scans and were excluded from further analysis. A total of 4560 internal carotid arteries were analysed in terms of symptoms. In a further 54 vessels the degree of stenosis was classified as "uncertain" and these together with 248 occluded arteries have been excluded from the principal analysis. Therefore, a total of 4258 internal carotid arteries with varying degrees of stenosis up to 99%, varying symptoms and varying plaque characteristics have been included in the main study.

Symptoms and Degree of Stenosis

Symptoms were analysed in 4560 bifurcations (Table 3). Symptoms attributable to the distribution of one internal carotid artery were present in 1324 (29.4%)

Table 3. Presenting symptoms and degree of stenosis

	Degree of stenosis								
	<20%	20–49%	50–79%	80–99%	Total	Occluded	Uncertain	Total	(%)
Symptomatic									
CVA	367	57	46	53	523	95	15	633	13.9
TIA	401	65	50	43	559	23	10	592	13.0
AF	53	3	9	20	85	8	0	93	2.0
CRAO	15	3	1	2	21	2	1	24	0.5
Total	836	128	106	118	1188	128	26	1342	29.4
Asymptomatic									
Normal	1167	114	38	23	1342	23	18	1383	30.3
ACB	291	207	163	109	770	87	4	861	18.9
Ver-bas	264	27	8	0	299	1	2	302	6.6
Non-haem	552	56	32	19	659	9	4	672	14.7
Total	2274	404	241	151	3070	120	28	3218	70.6
Study total	3110	532	347	269	4258	248	54	4560	

CVA = cerebro-vascular accident; TIA = transient ischaemic attack; AF = amaurosis fugax; CRAO = central retinal artery occlusion; ACB = asymptomatic carotid bruit; Ver-bas = vertebro-basilar insufficiency; Non-haem = non-haemispheric symptoms.

Table 4. Contingency table comparing the presence of symptoms related to the degree of internal carotid stenosis. The values in this table are derived from Table 3.

Stenosis	Symptomatic	Asymptomatic	Total
20–79%	234	645	879
80–99%	118	151	269
Total	352	796	1148

$\chi^2 = 28.0$; $p < 0.00001$

arteries. Of these, 118 (8.8%) had 80–99% stenosis and 128 (9.5%) had total occlusions. Symptoms were present in just over half (51.6%) of occluded vessels. Approximately two-thirds of symptomatic patients (62.3%) had effectively normal arteries with <20% stenosis. Amongst the asymptomatic patients 151 (4.7%) had 80-99% stenosis and 120 (3.7%) had occluded arteries. Just over two-thirds of asymptomatic patients (70.7%) had normal arteries.

Tight stenosis (80–99%) was significantly more likely to be associated with symptoms than lesser degrees (20–79%) of stenosis (Table 4, $\chi^2 = 28.0$, $p < 0.00001$). The numbers with each symptom are relatively small and no attempt has been made to make a detailed analysis of individual symptoms. However, from Table 3 it is apparent that 23.5% of stenoses presenting with amaurosis fugax were >80% whereas the similar figures for TIA and CVA are 7.7% and 10.1% respectively.

Plaque Type

Plaque was identified in 1558 bifurcations (36.6%) with a patent internal carotid artery (Table 5). The distribution of plaque type was 9.1% type I; 22.7% type II; 35.5% type III; and 32.7% type IV. Therefore, approximately one-third of plaques identified were heterogeneous (soft) and two-thirds homogenous (fibrous). Heterogeneous plaque was identified in 16% of all symptomatic vessels (Table 6) and 9.9% of asymptomatic vessels. The only symptom classification where heterogeneous types I and II plaque predominated was amaurosis fugax. For this condition 28 of 39 plaques (72%) occurring in a total of 85 bifurcations (33%) were of a heterogeneous nature (Table 7). The equivalent values for TIA were 39% and 13%, for CVA were 38% and 16% respectively (Table 7).

Plaque Type and Stenosis

There was a relationship between plaque type and the degree of stenosis (Table 7). Heterogeneous plaque types I and II were much more likely to occur at high grade stenoses. At <20% stenosis only 4.4% of plaques were heterogeneous, rising to 21.8% for 20–49% stenosis, 59.9% for 50–79% stenosis and 84.5% at 80–99% stenosis.

Plaque Type, Symptoms and Stenosis

Comparison of all three parameters simultaneously is complex and this has been summarised in Table 7. At all three grades of stenosis 20–49%, 50–79% and 80–99% there was no significant difference in the proportion of plaque types at each degree of stenosis when comparing symptomatic and asymptomatic vessels. Only in effectively normal arteries (<20% stenosis) was there an apparent difference ($p = 0.0397$).

Table 5. Summary of plaque types present with each symptom. Only patent internal carotid arteries are included (0–99%)

	Plaque type				Total with plaque	No plaque or not recorded	Total
	Type I	Type II	Type III	Type IV			
Symptomatic							
CVA	27	56	75	62	220	303	523
TIA	23	52	67	52	194	365	559
AF	15	13	5	6	39	46	85
CRAO	1	3	2	4	10	11	21
Total	66	124	149	124	463	725	1188
Asymptomatic							
Normal	19	48	152	147	366	976	1342
ACB	45	134	174	133	486	284	770
Ver-bas	1	9	22	28	60	239	299
Non-haem	10	39	56	78	183	476	659
Total	75	230	404	386	1095	1975	3070
Study total	141	354	553	510	1558	2700	4258
%	9.1*	22.7*	35.5*	32.7*	36.6†	63.4†	

* Percentage of total plaques seen (1558)
† Percentage of total patients (4258)

Table 6. Summary of proportion of internal carotid arteries with heterogeneous types I and II plaque for each symptom. Values summarised from Table 5

	Number with type I & II plaques	% of all plaques	% of total arteries
Cerebro-vascular accident (CVA)	83	37.7%	15.9%
Transient ischaemic attack (TIA)	75	38.7%	13.4%
Amaurosis fugax (AF)	28	71.8%	32.9%
All symptomatic arteries	190	41.0%	16.0%
All asymptomatic arteries	305	27.9%	9.9%

Discussion

One half (49.8%) of the vessels examined in this study had no evidence of disease nor any symptoms related to their anatomical distribution. The present data is therefore representative of a broad spectrum of people with varying degrees of atherosclerosis. One clear feature which emerges is that the two parameters of plaque morphology and degree of carotid stenosis are very closely related and probably inseparable. As the degree of stenosis increases, so the type of plaque changes from being a firm fibrous plaque to a more soft, haemorrhagic plaque (Table 7). This association is so strong, that neither plaque type nor stenosis can be considered to be a dominant factor and both must be considered to be equal determinants in the development of symptoms. This finding is in accordance with the view that the morphological changes found in carotid plaque may simply reflect the natural progression of atherosclerotic disease.[4, 5, 18, 19, 20, 21]

We have shown that plaque typing does not add to the sensitivity of stenosis in predicting the presence of symptoms. In particular, at high degrees of stenosis (>80%) there was no statistical difference in the plaque morphology of arteries that are symptomatic

Table 7. Comparison of totals of symptomatic and asymptomatic vessels with each degree of stenosis. For simplicity plaque types have been grouped as types I & II (heterogeneous) and III & IV (homogenous). Arteries which did not have plaque identified are not included

	<20% stenosis			20–49% stenosis			50-79% stenosis			80-99% stenosis		
Plaque type	I & II	III & IV	Total	I & II	III & IV	Total	I & II	III & IV	Total	I & II	III & IV	Total
Symptomatic	12	147	159	25	74	99	60	34	94	93	18	111
Asymptomatic	14	421	435	63	251	314	125	90	215	103	28	131
Total	26	568	594	88	325	413	185	124	309	196	46	342
%	4.4%	95.6%		21.8%	78.2%		59.9%	40.1%		84.5%	15.5%	
Statistics		$\chi^2 = 4.2$ $p = 0.04$			$\chi^2 = 0.9$ $p = 0.34$			$\chi^2 = 0.7$ $p = 0.42$			$\chi^2 = 0.73$ $p = 0.39$	

and those that are asymptomatic. Using the same plaque classification as ourselves Geroulakos *et al*[12] arrived at the opposite conclusion. In their study of vessels with a >70% stenosis they had 57 symptomatic and 30 asymptomatic type I & II plaques compared with 13 symptomatic and 43 asymptomatic type III & IV plaques ($\chi^2 = 24.4$, $p < 0.00001$). In our data we considered a higher degree of stenosis (>80%) and studied almost 100 more arteries (242 *vs.* 147, Table 7). The case selection in the study of Geroulakos *et al.* may also bias their results. A high proportion of their symptomatic patients had amaurosis fugax (53%). The equivalent value for our study was 19 of 111 arteries (17%). Our study has highlighted that amaurosis fugax may be a symptom with a much higher degree of association with soft plaques than is seen with other symptoms (Table 6).

The principal criticism of our data must be that it is a single temporal observation in what is a dynamic process. At present we do not know what proportion of asymptomatic vessels with a high grade stenosis and heterogeneous plaque will subsequently develop symptoms. It has been suggested in two prospective studies that many patients with soft, heterogeneous plaque do develop symptoms.[7,13] Johnston *et al.*[7] reported that in >75% stenosis with soft plaque there was a 74% TIA rate and 19% stroke rate over 3 years. The same patients when followed up for 5 years showed a 100% symptom rate.[16] In this same study, irrespective of plaque type, the cumulative symptom rate for >75% stenosis was 60%. Conversely, they reported a 20% cerebral complication rate over 3 years in patients with soft plaques and <75% stenosis. Therefore, although plaque type was undoubtedly important, it could be argued that the development of symptoms may to some extent have been attributable to the high degree of stenosis or disease progression rather than plaque type. Certainly, it would appear that heterogeneous plaque alone is not predictive of symptomatology.

Belcaro *et al.*[13] looked prospectively at plaque type in asymptomatic low grade stenosis (<60%). This data is difficult to put in context because they use a different method of plaque classification. In what they classify as "complex" plaques with calcification and ulceration there was a 24% cerebral complication rate and predominantly echolucent plaques were associated with an 8% cerebral complication rate over 4 years. Unfortunately, their plaque classification does not equate well to our own nor is it in accordance with the findings of Johnson *et al.*[7] who found a very low overall cerebral complication rate in their calcified plaques with <75% stenosis.

The mechanisms by which extracranial internal carotid disease produces the symptoms of both transient ischaemic attack and stroke are still poorly understood. Theories usually fall into one of two explanations, either that symptoms are the result of hypoperfusion in which case the degree of haemodynamically significant stenosis is important[22] or, more topically, that symptoms are the result of embolisation[7–17] in which case plaque type may be the more dominant factor. The role of intra-plaque haemorrhage in the development of symptoms is also controversial. It has been suggested that haemorrhage into a plaque heralds the onset of symptoms[8,11]. Others consider that haemorrhage is simply one element in the complex pathogenesis of atheroma and although it is present in the majority of symptomatic plaques the timing of haemorrhage does not always relate to the onset of symptoms.[20,21,23]

We, like others, have found it difficult to directly relate symptoms to plaque morphology.[5] Similarly, although symptoms are more frequently encountered with higher grade stenosis[5] there are also those who find degree of stenosis is a poor prognostic indicator.[20] This is supported by our finding that only half of our occluded arteries were associated with any symptoms.

A lack of consensus on the issues of aetiology of symptoms and the relative importance of plaque morphology and stenosis in producing these symptoms suggests that neither is necessarily the prime determinant. The present data would suggest that both plaque type and stenosis are interrelated and may be reflections of atherosclerotic disease severity. This is supported by the rather surprising finding from a number of prospective studies that those with haemorrhagic type plaques are at a higher risk of death from myocardial infarction than they are of stroke.[3,4,6,13]

If plaque type and stenosis are both reflections of disease severity, we should possibly be seeking different variables with which to select our high risk asymptomatic patients for surgery. Peak systolic velocity and end diastolic velocity are potential prognostic indicators.[19] Symptoms are significantly higher in patients with an end diastolic velocity of >200cm/s. A peak systolic velocity in excess of 420cm/s is associated with a high proportion of haemorrhagic plaques.[19] It has been postulated that these high flow rates induce shear stresses in the arterial wall as a result of the Bernoulli effect which lead to haemorrhage in the wall.[19] Systolic blood pressure is a determinant of peak systolic velocity and careful control of hypertension is a variable which requires close monitoring. This is clearly borne out by the influence of adequate anti-hypertensive control in

reducing stroke rate.[24, 25] A further variable that may add to the sensitivity of selection of patients for surgery is cerebrovascular reserve.[26] It is known that those people with a reduced cerebrovascular reserve have an increased susceptibility of cerebral infarction.[26, 27]

We must conclude that carotid plaque morphology is a reflection of the severity of atherosclerosis rather than a prime determinant in the development of symptoms. It is possible that long-term follow-up of large numbers of heterogeneous plaques may show that this may be a predictive factor for stroke. However, at present the place of plaque typing in the selection of patients for elective carotid surgery remains uncertain. Careful analysis of the flow dynamics in the carotid vessel, systolic and diastolic blood pressure combined with accurate monitoring of both cerebrovascular reserve and general cardiovascular performance may lead to better selection of high-risk patients with carotid disease.

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