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# Factors predicting compensatory vascular remodelling of the carotid artery affected by atherosclerosis

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**Objective:** To investigate factors predicting the development of outward remodelling of the carotid artery in patients with atherosclerosis.

**Design:** 130 patients with carotid artery stenosis (15–85% of the vessel diameter) were divided into two groups, based on the presence or absence of outward remodelling of the sclerotic carotid segment on high resolution ultrasonography. Logistic regression analysis was used to evaluate the contribution of haemodynamic, laboratory, and clinical measurements on the development of remodelling, including age, sex, type of stenosis, extent of plaque, per cent diameter stenosis, underlying disease, selected drug treatment, and plasma concentrations of total cholesterol, high density lipoprotein cholesterol, triglyceride, and uric acid.

**Results:** 64 patients (49%) had outward remodelling. Multivariate regression analysis showed that hypertension, the type of plaque, the thickness of the plaque, and the extent of stenosis were independent factors predicting remodelling. The odds ratios of hypertension, unstable shape of plaque, thickness of plaque, and the extent of the stenosis were 6.70, 3.02, 2.04, and 1.05, respectively. Other measurements did not contribute significantly to the estimation of remodelling.

**Conclusions:** Compensatory enlargement of the vessel occurs in about 50% of carotid artery segments with a diameter stenosis of 15–85%. Hypertension and the shape of the plaque are major determinants of the development of outward remodelling.

It has become apparent that blood vessels can enlarge to accommodate atheromatous plaques, forestalling encroachment on the lumen and hence preserving distal flow. Glagov and colleagues were the first to describe this process in the left main coronary artery in necropsy specimens.[1] The findings were confirmed clinically in femoral[2] and coronary arteries,[3] using intravascular and epicardial ultrasonography, and in the carotid artery by body surface ultrasonography. This "outward remodelling" consists of a spectrum of structural changes whereby the vascular wall responds to alterations in its haemodynamic environment. Smoking,[4] aging,[5] and hypercholesterolaemia[6] are also thought to be involved in the development of outward vascular enlargement. However, although attempts have been made to investigate the factors participating in compensatory vascular reconstruction, the mechanism of this type of remodelling remains obscure. Our aim in this study was to determine the prevalence of vascular remodelling and to investigate the factors leading to outward remodelling in the atherosclerotic carotid artery, using high resolution cross sectional ultrasonography.

## METHODS

### Subjects

The study population consisted of 165 consecutive patients with 15–85% diameter stenosis of the carotid artery system, determined by B mode ultrasonographic examination. Exclusion criteria were as follows: a major attack of coronary or cerebrovascular disease within one month of the investigation; overt congestive heart failure; cardiogenic shock; loss of consciousness; significant infectious disease; previous carotid surgery or stenting. Patients over 85 years of age were also excluded from the study. Laboratory data were obtained within one week on either side of the ultrasonographic examination.

### Ultrasonographic measurement

A Toshiba high resolution ultrasound unit (Sonolayer SSA-270A, Toshiba, Tokyo, Japan) equipped with a 7.5 MHz transducer was used to scan the carotid artery. Images were transcribed as hard copy with a digitised pad interfaced to a personal computer running custom designed ultrasound analysis software. Patients were examined in the supine position with slight hyperextension of the neck.

Sequential perpendicular cross sections along the axis of the vessel and parallel longitudinal sections from the medial to the lateral vascular wall were scanned. Each scan of the common carotid artery began just above the clavicle, and the transducer was moved cephalad through the bifurcation and along the extracranial internal carotid artery. Each carotid wall segment was interrogated independently from continuous angles to identify the plaque or thickest intima–media site.

An arterial plaque was defined as an echogenic structure encroaching on the vessel lumen with a wall thickening greater than 150% of the surrounding, relatively normal wall thickness.[7] The minimum lumen and interadventitial diameters at the plaque site were measured for calculating the per cent diameter stenosis of the vessel. The extent of the plaque was defined as the maximum distance from the luminal end to the adventitia at the plaque site. All diameters were measured during diastole, which was determined as the end of the T wave on the ECG, to avoid image blurring caused by arterial wall motion in systole. The most severely affected site in either the right or the left carotid artery was used for analysis.

The lesions were categorised into one of two types—stable or unstable—based on the morphology of the plaque, as previously reported.[8] Briefly, multiple stenoses or eccentric stenosis with a narrow neck (caused by one or more overhanging edges or an irregular or scalloped border, or both) defined the unstable type; plaque with concentric stenosis or eccentric stenosis

**Abbreviations:** ACE, angiotensin converting enzyme; HDL, high density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A

**Table 1** Reproducibility of the results

| | First observer | | |
|---|---|---|---|
| | First measurement | Second measurement | Second observer |
| *Common carotid artery* | | | |
| Plaque thickness (mm) | 3.10 (0.92) | 3.13 (0.94) | 3.13 (0.97 |
| Minimum lumen diameter (mm) | 4.68 (1.01) | 4.66 (1.25) | 4.62 (1.05) |
| Interadventitial diameter (mm) | 7.80 (1.61) | 7.83 (1.64) | 7.81 (1.53) |
| *Internal carotid artery* | | | |
| Plaque thickness (mm) | 2.51 (1.23) | 2.49 (1.29) | 2.51 (1.21) |
| Minimum lumen diameter (mm) | 3.02 (1.86) | 3.00 (1.85) | 3.03 (1.90) |
| Interadventitial diameter (mm) | 5.44 (1.05) | 5.42 (1.01) | 5.44 (1.08) |

Values are mean (SD).

without a narrow neck or irregular or scalloped border defined the stable type. Arterial segments with a diameter stenosis of less than 15% or more than 85% were excluded from the study because minimal or extremely severe obstruction made classification of the type of stenosis difficult.

Outward vascular remodelling was defined as follows:

- using parallel longitudinal images, the media–adventitia interface of the stenosis site protruded outside in comparison with the proximal segment where no or only minimal plaques were observed
- the diameter between the media–adventitia interface at the plaque site in perpendicular cross sections was greater by 0.5 mm or more than that of the proximal segment with no or minimal plaques.

### Reproducibility of the results

The reproducibility of the results for plaque thickness, minimum luminal diameter, and interadventitial diameter was assessed in seven patients with significant stenotic plaques in the common carotid artery and in seven with a stenosis in the internal carotid artery. Intraobserver variability was defined by one observer making duplicate measurements with an interval of 7–14 days, and interobserver variability was defined by another observer making a single set of measurements. The interobserver and intraobserver variability of the morphological classification of plaques was tested in a similar manner.

### Statistical analysis

Data are expressed as mean (SD). SAS software (SAS Institute Inc, Cary, North Carolina, USA) was used for data analysis. Independent dichotomous variables were compared between the presence and absence of vascular remodelling using $\chi^2$ analysis, and continuous variables using Student's $t$ test for unpaired data. The influence of various factors on remodelling was investigated by multiple logistic regression analysis. The factors considered were age, sex, morphology of the plaque, plaque thickness, the extent of stenosis, serum total cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, uric acid, underlying disease, smoking, and drug treatment, including HMG-CoA reductase inhibitors, nitrates, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, aspirin, and oral antidiabetic agents.

## RESULTS

### Reproducibility of the results

Two ultrasonographic measurement with an interval of 7–14 days confirmed the good reproducibility of the variables measured, as shown in table 1. The mean difference between the two measurements of each variable was less than 7%. When another observer recorded ultrasonograms of the carotid artery just after the second measurement by the first observer, the difference between the two observers was also less than 7% for each variable. Of 14 lesions, one observer classified six plaques as unstable and eight as stable in the first assessment, and the result of the second assessment by the same observer was entirely consistent with the first measurement. Another observer assessed five lesions as belonging to stable group and the remaining nine as unstable. Only one lesion was classified in a different group from that determined by the first observer.

### Patient characteristics

Of 165 segments with an atherosclerotic lesion causing an obstruction of 15–85% of the lumen diameter, 35 segments were excluded from the study because of inadequate ultrasound images—for example, images with shadowing or loss of definition posterior to strongly reflective calcifications are difficult to trace accurately. The remaining 130 segments were used for analysis. Seventy eight lesions were in the common carotid artery and 52 in the internal carotid artery.

Table 2 shows the clinical characteristics of the subjects. Blood glucose concentrations in diabetic patients were well controlled by diet and appropriate drugs. Systemic hypertension was considered to be present if there was an apparent history of high blood pressure, regardless of drug treatment, or if physical examination showed raised systolic or diastolic blood pressure, or both (persistently more than 140/90 mm Hg). Hyperlipidaemia was defined as a laboratory documented increase in total serum cholesterol (> 5.7 mmol/l) or triglyceride (> 1.7 mmol/l), or both. Arterial blood pressure in all hypertensive patients was controlled below 140/90 mm Hg by drug treatment. Twenty five subjects (19%) had a serum cholesterol concentration above 5.7 mmol/l despite taking an HMG-CoA reductase inhibitor (statin), and abnormally low HDL cholesterol concentrations (≤ 1.04 mmol/l) were observed in 42 patients (32%). Serum triglyceride concentrations were more than 1.7 mmol/l in 38 patients (29%).

### Remodelling related factors

Outward remodelling in the carotid artery system was identified in 64 patients (remodelling group) and was considered absent in the remaining 66 subjects (non-remodelling group). The mean age and sex distribution did not differ between the two groups. Maximum plaque thickness ($p = 0.020$), the extent of stenosis ($p = 0.025$), the prevalence of unstable plaque ($p = 0.009$), and the prevalence of hypertension ($p = 0.0003$) were significantly increased in the remodelling group (table 2). There was no significant difference in serum total and HDL cholesterol, triglyceride, or uric acid concentrations between the two groups. The prevalences of hyperlipidaemia, diabetes mellitus, ischaemic heart disease, and a history of cerebrovascular accidents did not differ between the two groups. Smoking did not influence the prevalence rate of vascular remodelling. There was no effect of drug treatment with statins, nitrates, calcium channel blockers, ACE inhibitors, aspirin, or oral antidiabetic agents on the occurrence of remodelling.

**Table 2** Clinical characteristics of the subjects

| | Remodelling (+) (n=64) | Remodelling (–) (n=66) | p Value |
|---|---|---|---|
| Age (years) | 70 (8) | 68 (10) | 0.186 |
| Sex | | | 0.496 |
| Men | 40 (63%) | 45 (68%) | |
| Women | 24 (37%) | 21 (32%) | |
| Morphology of plaques | | | 0.009 |
| Unstable type | 35 (55%) | 21 (32%) | |
| Stable type | 29 (45%) | 45 (68%) | |
| Thickness of plaque (mm) | 3.57 (1.13) | 2.63 (0.90) | 0.013 |
| Extent of stenosis (%) | 44.2 (18.4) | 34.5 (16.5) | 0.002 |
| Laboratory data | | | |
| Total cholesterol (mmol/l) | 5.34 (0.98) | 5.21 (1.09) | 0.419 |
| HDL cholesterol (mmol/l) | 1.22 (0.36) | 1.22 (0.36) | 0.951 |
| Triglyceride (mmol/l) | 1.54 (0.76) | 1.44 (0.66) | 0.413 |
| Uric acid (mmol/l) | 0.33 (0.09) | 0.34 (0.10) | 0.777 |
| Underlying diseases | | | |
| Hypertension | 51 (80%) | 32 (48%) | 0.0003 |
| Hyperlipidaemia | 26 (41%) | 20 (30%) | 0.219 |
| Diabetes mellitus | 15 (23%) | 19 (29%) | 0.488 |
| Ischaemic heart disease | 38 (59%) | 37 (56%) | 0.702 |
| Smoking | 24 (38%) | 31 (47%) | 0.275 |
| Drug treatment | | | |
| HMG-CoA RI | 24 (38%) | 23 (35%) | 0.650 |
| Nitrates | 35 (55%) | 33 (50%) | 0.593 |
| Calcium channel blocker | 44 (69%) | 38 (56%) | 0.187 |
| ACE inhibitor | 16 (25%) | 16 (24%) | 0.920 |
| Aspirin | 45 (70%) | 41 (62%) | 0.324 |
| Oral antidiabetic agents | 13 (20%) | 15 (23%) | 0.738 |

Values are mean (SD) or n (%).
ACE, angiotensin converting enzyme; HDL, high density lipoprotein; HMG-CoA RI, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor.

Multivariate analysis (table 3) showed that four measurements—the morphologic type of the plaque, maximum plaque thickness, the extent of stenosis, and hypertension—were independent factors predicting adaptive outward remodelling. Among these four variables, the odds ratio of hypertension, calculated in the presence of the other covariables, was highest (6.70, 95% confidence interval (CI) 2.42 to 18.00; $p = 0.0002$), while that of the degree of diameter stenosis was lowest (1.05, 95% CI 1.006 to 1.068, $p = 0.025$); the odds ratios of morphologically unstable plaque and plaque thickness were intermediate.

**Table 3** Logistic regression analysis

| Variable | Odds ratio | 95% CI | p Value |
|---|---|---|---|
| Age | 1.05 | 0.98 to 1.11 | 0.155 |
| Sex (male) | 2.60 | 0.80 to 8.47 | 0.111 |
| Unstable type of plaque | 3.11 | 1.15 to 8.41 | 0.025 |
| Thickness of plaque | 2.04 | 1.07 to 4.50 | 0.020 |
| Extent of stenosis | 1.05 | 1.01 to 1.07 | 0.025 |
| Laboratory data | | | |
| Total cholesterol | 1.01 | 0.99 to 1.02 | 0.223 |
| HDL cholesterol | 0.98 | 0.95 to 1.01 | 0.233 |
| Triglyceride | 1.00 | 0.99 to 1.01 | 0.952 |
| Uric acid | 0.89 | 0.65 to 1.21 | 0.442 |
| Underlying diseases | | | |
| Hypertension | 6.70 | 2.42 to 18.00 | 0.0002 |
| Hyperlipidaemia | 2.40 | 0.82 to 7.01 | 0.109 |
| Diabetes mellitus | 0.36 | 0.12 to 1.03 | 0.056 |
| Ischaemic heart disease | 2.00 | 0.79 to 5.06 | 0.141 |
| Smoking | 0.45 | 0.15 to 1.36 | 0.158 |
| Drug treatment | | | |
| HMG-CoA RI | 2.52 | 0.98 to 6.48 | 0.056 |
| Nitrates | 2.21 | 0.87 to 5.62 | 0.095 |
| Calcium channel blocker | 1.64 | 0.65 to 4.15 | 0.298 |
| ACE inhibitor | 1.75 | 0.60 to 5.06 | 0.306 |
| Aspirin | 1.49 | 0.58 to 3.82 | 0.404 |
| Oral antidiabetic agents | 0.96 | 0.33 to 2.82 | 0.947 |

## DISCUSSION

As the assessment of the media–adventitia boundary is highly reproducible with high resolution cross sectional scanning,[9] we used the maximum interadventitial diameter as a measure of arterial enlargement. Some investigators who have used intravascular ultrasonography for assessing coronary remodelling have measured the cross sectional areas of the atheroma and the artery.[10 11] Although cross sectional area is supposed to be a sensitive measure of vascular enlargement, the interadventitial diameter is also sensitive enough to assess vessel enlargement, because of the round form of the artery in cross section. Moreover, it is much easier—and therefore more reproducible—to measure the interadventitial diameter than the cross sectional area.

### Prevalence rate

Out study showed that about half the carotid arteries with a 15–85% atherosclerotic obstruction had adaptive outward remodelling. Tauth and colleagues classified the shape of remodelling using intravascular ultrasonography in the coronary artery, and observed that about one third of remodelling was outward.[6] The prevalence of outward remodelling in our study was greater than that. As coronary atherosclerosis develops, on average, earlier in life than carotid atherosclerosis,[12] a higher prevalence rate of outward remodelling in the carotid artery than in the coronary artery is unexpected. Although we could not determine the reason for this finding, the extent of the atherosclerosis may be relevant. We analysed the carotid artery in segments with mild to moderate stenosis, while Tauth studied coronary arteries with severe stenosis requiring angioplasty. Another explanation might be that the common carotid artery and the coronary artery are structurally different, representing elastic and muscular vasculature, respectively.[13] A third possibility could be a different prevalence of hypertension in the study subjects in the two investigations: although we could not make a direct comparison of the contribution of hypertension to vascular remodelling in Tauth's study, because the prevalence of hypertension

was not specified, it is possible that more of the patients in our study were hypertensive than in Tauth's study.

### Predictors of remodelling

Our study showed that hypertension was a highly significant predictor of local vascular enlargement in carotid arteries containing atheromatous plaques. Kiechl and Willeit,[9] in a five year follow up study, found that hypertension was a factor in the regulation of vascular diameter during medical lowering of LDL cholesterol by statin treatment. It is conceivable that raised blood pressure causes dilatation of exposed arteries. Nakaki and Kato,[14] using the strip artery model, observed that pressure promoted cell proliferation and DNA synthesis in a pressure dependent manner. The findings suggest a significant role for active medial proliferation in hypertension induced vascular dilatation. Although the effect of hypertension may explain the geometric changes in the vessel overall, it does not fully account for localised remodelling limited to certain portions of the vessel affected by atheroma. Thus the mechanism of localised outward dilatation in atheromatous segments is still unknown.

Losordo and colleagues compared the internal elastic lamina area of cross sections obtained from an atherosclerotic femoral artery segment and a non-diseased proximal cross section.[15] They found an increase in the internal elastic lamina area in the atherosclerotic cross section that paralleled the increase in atheroma area. In contrast, Berglund and his co-workers[3] failed to show a significant difference in maximum area stenosis in the coronary artery, regardless of whether there was eccentric or concentric atherosclerosis. In our study, the plaque was significantly thicker in the group with vascular enlargement than in the group without remodelling. Hennerici and his associates[16] determined the ultrasound characteristics of five types of plaque, and observed that fibrous and hard plaques remained unchanged or progressed slightly after 18 months of follow up, while spontaneous regression was observed mainly in soft plaques and ulcerative lesions. The results suggest that the latter two are unstable lesions. Though our morphological classification of plaques was different from Hennerici's, soft plaques and ulcerative lesions would certainly represent unstable plaques in our study. Weinberger and colleagues[17] observed that there was a greater incidence of symptoms with mural plaques that increased in size than with those that tended to regress. We were unable to comment on the relation between morphological change in the plaques and clinical symptoms in our study, because we did not do repeated measurements at an interval sufficient to assess any morphological changes in the plaques. The degree of diameter stenosis in the remodelling group varied over a wide range, with a mean of 44 (18)%, and was approximately 10% greater than in the group without remodelling. However, multivariate analysis showed only a limited contribution of the dimension of plaque thickness and the extent of the stenosis to the regulation of outward remodelling. This suggests that major factors other than plaque size are participating in the compensatory structural changes.

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