Major Variation in Carotid Bifurcation Anatomy
A Possible Risk Factor for Plaque Development?

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Background and Purpose—Why is carotid plaque often so strikingly asymmetrical within individuals, and why does the extent of disease vary so considerably between individuals with similar systemic risk factors? Variability of carotid bifurcation anatomy is a possible explanation. Flow models suggest that vessel anatomy, in particular vessel diameter and area ratios, affects plaque formation at arterial bifurcations. However, carotid bifurcation anatomy could only be a major risk factor for plaque formation if it was sufficiently variable. Since very few data exist on the extent of interindividual and intraindividual variability of bifurcation anatomy, we studied 5395 angiograms from the European Carotid Surgery Trial.

Methods—To minimize changes in bifurcation anatomy secondary to atherosclerosis, we excluded vessels with ≥30% stenosis. We measured arterial diameters at disease-free points and calculated the following ratios: internal to common carotid (ICA/CCA), external to common carotid (ECA/CCA), external to internal carotid (ECA/ICA), and outflow/inflow area. For intraindividual asymmetry, we compared the ratios on both sides.

Results—Each ratio varied markedly between individuals. The 95% ranges were as follows: ICA/CCA, 0.44 to 0.86; ECA/CCA, 0.34 to 0.80; ECA/ICA, 0.55 to 1.33; and outflow/inflow area, 0.38 to 1.28. The results were very similar in 407 bifurcations with no disease. Among the 755 patients with ≥30% stenosis bilaterally, side differences of ≥25% were present in 17% (95% CI, 15% to 20%) for the ICA/CCA ratio, 27% (95% CI, 24% to 30%) for the ECA/CCA ratio, 32% (95% CI, 28% to 35%) for the ECA/ICA ratio, and 42% (95% CI, 38% to 45%) for the outflow/inflow area ratio.

Conclusions—We found large interindividual differences in carotid bifurcation anatomy. For example, there was 4-fold variation of the ratio of outflow to inflow area. Intraindividual variation was also considerable. These data highlight the potential importance of anatomic variation as a risk factor for atheroma and provide a firm basis for flow modeling studies. (Stroke. 2001;32:2522-2529.)

Key Words: angiography • carotid arteries • risk factors • stroke

The carotid bifurcation is one of the most common sites of atherosclerotic plaque. However, there is considerable variation, both between and within individuals, in the development of plaque. Given the same systemic risk factors for atheroma, why do some people develop carotid atheroma, while others develop ischemic heart disease or peripheral vascular disease? Why does plaque tend to develop very focally around the bifurcation, rather than in other parts of the carotid artery? How is it possible, when the systemic risk factors for atherosclerosis should affect both bifurcations equally, that the extent of carotid plaque is often so asymmetrical within individuals? One possible explanation for these observations is that vessel anatomy influences plaque development.

Several studies have developed flow models to investigate the possible relationship between bifurcation anatomy, hemodynamics, and atheroma. They suggest that vessel diameter and area ratios are potentially important determinants of plaque development. However, this could only explain the considerable variation in plaque formation at the carotid bifurcation if anatomy varied significantly between and within individuals. Very few studies have investigated this. All have been small and were concerned mainly with absolute vessel sizes rather than vessel diameter and area ratios, which have been suggested to be more important. The study that did examine vessel ratios was far too small (61 patients) to determine the full extent of anatomic variation reliably.

Our aim was to determine the extent of variation in carotid bifurcation anatomy within and between individuals by reviewing the 5395 angiograms from 3007 patients in the European Carotid Surgery Trial (ECST). The advantages of this population were that it was sufficiently large (>10 times larger than all previous studies combined) to provide the necessary statistical power and that all patients had undergone angiography (usually conventional selective arterial angiography), allowing accurate and reliable measurement of the vessel lumen. The disadvantage was that they were a...
selected group of mainly elderly individuals with established vascular disease. It has been shown that vessel diameters increase with age and also depend on the presence of vascular risk factors, such as hypertension. A population-based study using angiography would be unethical, and studies using Doppler or MR angiography would not allow such accurate measurements of all the bifurcation vessels. MR angiography is less accurate than arterial angiography, and Doppler is often not able to image the internal carotid artery (ICA) distal to the bulb. Thus, a large angiography-based study in a selected population would probably provide more reliable data on the extent of variation in carotid bifurcation anatomy than a smaller noninvasive, imaging-based study in the general population.

Subjects and Methods

We studied the carotid angiograms of patients randomized in the ECST. The methods and results of this trial and the details of the angiographic technique have been published previously. Briefly, patients with recent ocular or carotid territory cerebral ischemia, who had evidence of carotid stenosis on an angiogram, were randomized to carotid endarterectomy and best medical treatment versus best medical treatment alone. Baseline clinical data were recorded, and patients were followed up by a physician at 4 months, 12 months, and annually thereafter. Of 3018 patients randomized in the trial, 3007 (99.6%) had angiograms of the symptomatic carotid artery, and 2388 (79.4%) had contralateral carotid angiograms available for study.

Selection of Angiograms

All the patients included in the ECST had some atheromatous disease in at least 1 carotid artery. Severe atheromatous disease can lead to secondary changes in vessel anatomy. For example, blood pressure and blood flow decrease beyond a stenosis of ≥80%, and the ICA narrows distal to a stenosis of ≥70%. In contrast, changes in blood flow or pressure do not occur distal to lesions of <50%, and there is no poststenotic narrowing. To minimize the secondary effects of atheromatous disease, we therefore excluded angiograms with ≥30% stenosis of the ICA or common carotid artery (CCA) (by North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria; ≥50% by ECST criteria). The reproducibility of this measurement and its equivalence with other methods have been reported previously. For analysis of variability between individuals, all patients with a stenosis of <30% were included. To avoid double counting of individuals with a bilateral stenosis of <30%, we only included the artery contralateral to the symptomatic side in this analysis. To study variation in bifurcation anatomy within individuals, we included only patients with bilateral <30% ICA or CCA stenosis.

More than 97% of patients had arterial angiograms, and the remainder had intravenous digital angiography. Angiograms were obtained at many different centers. Consequently, projection angles, magnification factors, type of angiography, and image quality were not standardized. To examine the possibility that apparent variation in bifurcation anatomy might be caused by differences in the acquisition and quality of the angiograms, we assessed whether variation differed in the following categories: angiographic view (lateral, oblique, anterior); number of views available; method of image acquisition (conventional, digital); angiographic technique (selective, aortic arch injection, intravenous injection in <3% of patients); and image quality (good, adequate, poor).

Assessment of Bifurcation Anatomy

Because of their potential importance in the development of atheroma, we studied the vessel diameter and area ratios. Since the angiograms were not standardized, it was not possible to study absolute vessel sizes or the bifurcation angle. However, use of ratios eliminated the magnification factor of the angiograms and, if it is assumed that the blood vessel cross sections were approximately circular, produced results that were independent of the projection angle. Hence, use of vessel ratios enabled us to compare nonstandardized angiograms from different centers.

We studied the relative sizes of CCA, ICA, and external carotid arteries (ECA). The diameter of the ICA was measured distal to the bulb, at a disease-free section where the walls were parallel. The diameters of the other arteries were also measured at representative, disease-free sections with parallel walls (Figure 1). Measurements were made by a single observer (P.M.R.) on all available angiograms of symptomatic (ipsilateral) and contralateral carotid arteries. All measurements were made with a jeweler’s eyepiece graduated in tenths of millimeters on the single angiographic film that showed the maximum stenosis. We recorded whether this was a lateral, anteroposterior, or oblique view. The symptomatic (ipsilateral) side was defined as described previously. We calculated the ratios of the diameters of the following arteries: ICA/CCA, ECA/CCA, and ECA/ICA. We also calculated the ratio of the outflow to inflow area, calculated as (ICA² + ECA²)/CCA².

Since apparent variations in the vessel dimensions could result from poor measurement technique, we assessed the reproducibility of angiographic measurements. We selected the ICA/CCA ratio as a representative measurement. Intraobserver agreement was assessed on 100 randomly selected angiograms measured 1 month apart (P.M.R.), and a second independent observer measured the ICA/CCA ratio on a consecutive series of 976 of the study angiograms to determine interobserver agreement.

Statistical Analysis

To determine interindividual variability, we calculated the interquartile ranges of the population distribution for each vessel ratio. If the ratios were normally distributed, we also calculated the 95% range as 1.96 SD above and below the mean. To assess intraindividual variation in bifurcation anatomy, we divided each vessel ratio on the ipsilateral side by its contralateral counterpart. For the resulting ratios we calculated the mean, interquartile range, and 95% range. In addition, we determined the percentage of patients in whom a given ratio differed by ≥25% between the 2 sides. We also correlated the vessel diameter ratio and area ratio on the ipsilateral side with that on the contralateral side, using the squared Pearson correlation coefficient for parametric data. To assess whether there were any systematic differences in bifurcation anatomy between the left and the right sides within individuals, we performed a paired t test for all vessel diameter and area ratios. The following baseline characteristics were collected in the ECST: age, sex, smoking, systolic and diastolic blood pressure, cholesterol,
hemoglobin, hematocrit, urea, blood glucose, antihypertensive therapy, cardiac failure, presentation with lacunar versus nonlacunar symptoms, history of angina, history of myocardial infarction, history of peripheral vascular disease, and occurrence of transient ischemic attack, amaurosis fugax, retinal artery occlusion, and minor or major stroke before randomization. To compare whether the variability of the vessel ratios was related to the baseline characteristics, we performed Levene’s test for homogeneity of variances.27

Statistical analysis was performed with the use of SPSS for Windows, version 9.0.

### Results

Of the 5395 angiograms, 2930 had carotid stenosis of <30%. A total of 1420 patients had unilateral ICA or CCA stenosis of <30%, and 755 patients had ICA or CCA stenosis of <30% bilaterally. Thus, the analysis of interindividual variation in carotid bifurcation anatomy was based on 2175 patients (1420 patients with unilateral stenosis of <30% plus 755 patients with bilateral ICA stenosis of <30% for whom only the asymptomatic side was included) and the analysis of intraindividual variability on 755 patients.

Measurements of the vessel lumen diameter ratios were highly reproducible. Intraobserver reproducibility for the ICA/CCA ratio on 100 angiograms was good (intraclass correlation coefficient = 0.82; 95% CI, 0.73 to 0.91), and there was no systematic bias between the first and second measurements. Measurements differed by >25% in only 7 cases (7%). Interobserver agreement in measurement of the ICA/CCA ratio on the 976 independently assessed angiograms was also good (intraclass correlation coefficient = 0.79; 95% CI, 0.76 to 0.82). Measurements differed by >25% in 93 (9.5%) of cases.

### Variation in Bifurcation Anatomy Between Individuals

We found no systematic differences in any of the calculated ratios between left and right bifurcations within individuals. Side was therefore not taken into account in the analysis of variation between individuals. Table 1 shows the mean values, interquartile ranges, and 95% ranges of the vessel diameter ratios and the ratio of outflow/inflow area. They show considerable variation. The 95% ranges were as follows: ICA/CCA, 0.44 to 0.86; ECA/CCA, 0.34 to 0.80; ECA/ICA, 0.55 to 1.33; and outflow/inflow area, 0.38 to 1.28. Thus, the normal range, for example, the ECA diameter varied from being almost half that of the ICA to being more than a third larger than the ICA. The normal range of the outflow area (the sum of the cross-sectional areas of the ECA plus the ICA) varied from being 62% less to being 28% more than the inflow area (the cross-sectional area of the CCA). Examples of such bifurcations are shown in Figure 2.

Figure 3 shows the distribution of measurements for each vessel diameter ratio and the ratio of outflow to inflow area. These figures also show that we found very similar results when we restricted the analysis to the 407 bifurcations with no evidence of atheromatous disease (Table 1). The variability of the ICA/CCA ratio was greatest in patients presenting with eye symptoms only (SD = 0.11; 95% range, 0.43 to 0.87) and smallest in hypertensive patients (SD = 0.11; 95% range, 0.43 to 0.84). The variability of the outflow to inflow area ratio was greatest in normotensive patients (SD = 0.25; 95% range, 0.24 to 1.22) and smallest in hypertensive patients (SD = 0.23; 95% range, 0.27 to 1.16). However, none of these differences in the degree of anatomic variation were statistically significant (P > 0.1 for all baseline characteristics, Levene’s test). Overall, the interindividual variability of the vessel diameter and area ratios was independent of all baseline characteristics and of all potential angiographic confounders.

### Variation in Bifurcation Anatomy Within Individuals

Bifurcation anatomy also showed considerable variability within individuals. The scattergrams in Figure 4 show the variation in vessel ratios between the ipsilateral and the contralateral sides. Although we found positive correlations between the vessel ratios on the different sides, and these were statistically highly significant (P < 0.0001) for all ratios, the strength of the correlations was actually very weak. The squared Pearson correlation coefficient varied between 0.12 for the ECA/ICA ratio and 0.16 for the ICA/CCA ratio.

Table 2 shows the extent of asymmetry within individuals. Side differences of ± 25% were present in 17% (95% CI, 15% to 20%) of patients for the ICA/CCA ratio, in 27% (95% CI,
24% to 30%) for the ECA/CCA ratio, in 32% (95% CI, 28% to 35%) for the ECA/ICA ratio, and in 42% of patients (95% CI, 38% to 45%) for the ratio of outflow to inflow area. Figure 5 shows the distribution of the degree of asymmetry between the different sides, ie, the variation of the ratio obtained by dividing a measurement on one side (ipsilateral bifurcation) by its counterpart on the other side (contralateral bifurcation).

**Discussion**

Our findings show that variation in carotid bifurcation anatomy is not restricted to differences in absolute vessel size. In addition, vessel diameter and area ratios vary markedly between and within individuals. For example, between individuals there was a 4-fold variation of the outflow to inflow area ratio.

**Potential Shortcomings of the Study**

Although we consider our findings to be valid, our study has some potential shortcomings. First, observations on normal anatomy should ideally be made on population-based cohorts.
The invasive nature of cerebral angiography forbids its use on healthy subjects, and it would therefore not have been possible to obtain our data in a population-based cohort. Our study was based on a clinical trial population with a history of carotid territory ischemic events, and our results will therefore not provide a precise estimate of the variation of carotid bifurcation anatomy in a general population. However, because the few previous studies have been so small, \(^{10-12}\) it has thus far been unclear whether carotid anatomy varies at all. Our study has shown that carotid anatomy varies considerably, to an extent that makes it unlikely that the choice of study population could have led to major distortions of the result.

Second, our study population consisted of elderly individuals with symptomatic cerebrovascular disease and a high prevalence of vascular risk factors. It has been shown that vessel diameters increase with age and also depend on the presence of vascular risk factors such as hypertension. \(^{16-18}\) However, since these factors are systemic they should affect both bifurcations similarly and within a bifurcation should affect each vessel to a similar extent, and they should only have a very small effect on anatomic variation. Moreover, we found no association between vascular risk factors and the extent of intraindividual or interindividual anatomic variation.

Third, a study on bifurcation anatomy should ideally only include bifurcations with no atheromatous disease, since carotid stenosis can lead to secondary changes in vessel anatomy. \(^{14,23-25}\) However, by excluding angiograms with \(\geq 30\%\) stenosis, we minimized such secondary effects. Moreover, our analysis of disease-free, contralateral bifurcations produced very similar results (Table 1).

Fourth, we used conventional cerebral angiography rather than Doppler or MR angiography to study vessel anatomy. Angiography only delineates the vessel lumen; it does not give any information about the thickness or stiffness of the vessel wall. We might therefore have missed early atheromatous changes such as intima-media thickening, which are associated with compensatory dilatation of the vessel \(^{16}\) and which might have been more prevalent in our population compared with a general population. This could have led to an overestimation of anatomic variation. However, in the absence of plaque, intima-media thickening only leads to small alterations in the vessel lumen \(^{16}\) and could only account for a very small part of the large variation that we found. For our study it was particularly important to obtain accurate

| TABLE 2. Variability of Bifurcation Anatomy Within Individuals* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | n    | Mean (95% CI) | SD  | Interquartile Range | 95% Range | Asymmetry \(\geq 25\%\) (95% CI)† | \(R^2\) (95% CI)‡ |
| ICA/CCA         | 755  | 1.00 (0.99–1.02) | 0.19 | 0.89–1.11 | 0.67–1.45 | 17% (15–20) | 0.16 (0.11–0.21) |
| ECA/CCA         | 755  | 1.02 (1.00–1.04) | 0.24 | 0.85–1.15 | 0.63–1.58 | 27% (24–30) | 0.14 (0.10–0.19) |
| ECA/ICA         | 755  | 1.04 (1.02–1.06) | 0.26 | 0.86–1.19 | 0.63–1.67 | 32% (28–35) | 0.12 (0.08–0.16) |
| Outflow/inflow area | 755 | 1.04 (1.01–1.06) | 0.35 | 0.81–1.21 | 0.50–1.88 | 42% (38–45) | 0.14 (0.10–0.19) |

*Calculated by dividing vessel ratios on the symptomatic side by their counterparts on the contralateral side in each individual. Data were derived from patients with \(<30\%\) ICA stenosis bilaterally.
†Asymmetry \(\geq 25\%\) refers to the percentage of individuals in whom a given ratio varied by \(\geq 25\%\) between the 2 sides.
‡Squared Pearson correlation coefficient of ratios on the symptomatic side correlated with ratios on the contralateral side.
measurements of the lumina of all 3 vessels of the bifurcation. Angiography is still the best method to show vessel lumina, and it also reliably shows the distal parts of the ICA, which is often difficult with Doppler.16,21 The distal parts of the vessels can also be shown with MR angiography. This technique is in constant development and, as a research tool, is currently used not only to provide images of blood vessels and plaque morphology but also to study hemodynamic patterns.28,29 However, for clinical purposes conventional angiography is still more accurate than MR angiography.19,20

Interindividual Variability of Carotid Bifurcation Anatomy

It is well recognized that the absolute size of the main branches of the carotid bifurcation varies between individuals.11,30,31 Vessel calibers correlate strongly with body height and body weight,30 men have larger vessels than women,31 and vessel size increases with age.16 However, we found that variation in carotid bifurcation anatomy was not restricted to differences in absolute vessel size. In addition, there was considerable variation of the arterial diameter ratios and arterial area ratios. For example, the normal range of the ECA varied between half that of the ICA and a third more, and there was a 4-fold variation of the ratio of outflow to inflow area. The extent of this variation has not been described before. A small angiographic study found relatively constant relationships between the diameters of the CCA and its distal branches.12 However, their study only included 61 patients and therefore did not have sufficient statistical power to determine the full extent of anatomic variation.

Intraindividual Variability of Carotid Bifurcation Anatomy

Previous studies of intraindividual asymmetry of the carotid bifurcation have reported conflicting results. A Doppler study of 53 healthy young subjects found no statistically significant side differences in absolute vessel sizes.30 An angiographic study of 142 patients found a side difference of ∼5% in the absolute caliber of the ICA in 35 of 142 patients.10 In our analysis of 755 patients, we found marked variation in the vessel diameter and area ratios of the carotid bifurcation within individuals. For example, in 42% of patients the ratio of outflow to inflow area varied by ∼25% between the 2 sides. The extent of this variability has not been described before and seemingly contradicts the previous studies. However, vessel ratios depend on the diameter of 2 or, for the outflow to inflow area on the squared diameters, of 3 vessels, and their extent of variation would therefore differ from that of single vessels. In addition, our study included a much larger number of patients than the previous studies and therefore had more statistical power to show any significant anatomic variation.

Implications of Variability in Carotid Bifurcation Anatomy

Flow models have highlighted the potential importance of hemodynamics in plaque development. Plaque tends to develop in areas with low wall shear stress, and changes in mural tensile stress can influence plaque formation by caus-
ing alterations in wall structure and metabolism.\textsuperscript{32} Hemodynamics are influenced by vessel anatomy,\textsuperscript{7,8,9,33–35} and it therefore seems likely that differences in vessel anatomy could result in differences in the development of atheroma. Indeed, a potential relationship between carotid bifurcation anatomy and the prevalence of atherosclerotic plaque has been suggested in a few small studies.\textsuperscript{36–38} In a postmortem study on 60 normal and 40 diseased carotid bifurcations, the mean ratio of outflow to inflow area was significantly smaller in diseased bifurcations.\textsuperscript{36} An angiographic study of 26 patients found that the degree of asymmetry of carotid plaque was associated with the degree of asymmetry of the ICA/CCA ratio.\textsuperscript{37} Another angiographic study of 20 patients with severe carotid stenosis found that the more severe stenosis tended to occur on the side with the smaller carotid bifurcation.\textsuperscript{38} These studies suggest that bifurcation anatomy may be associated with the extent of plaque, and they also imply that there are interindividual and intraindividual differences in bifurcation anatomy. However, they ignored the potential secondary effects of atheromatous disease on bifurcation anatomy, and it is therefore not possible to say whether in these studies anatomic characteristics caused plaque formation or whether atherosclerosis led to changes in bifurcation anatomy. A possible association between carotid bifurcation anatomy and plaque development would have to be investigated in a longitudinal study. Because of the large number of potential confounders, such a study would have to be of considerable size to yield a reliable and accurate result. It would clearly only be of interest if anatomic variation was considerable, but thus far the extent to which carotid bifurcation anatomy varies has been unknown. Our study has shown that carotid anatomy is indeed very variable. It highlights the potential importance of bifurcation anatomy as a risk factor for plaque development and forms a firm basis for further flow modeling studies and longitudinal cohort studies of the relationship between vessel anatomy and plaque formation.

Conclusions

Variability in carotid bifurcation anatomy is not limited to differences in absolute vessel size. Vessel diameter ratios and vessel area ratios vary considerably between and within individuals. The extent of this variation has not been shown before. Flow models have suggested that carotid bifurcation anatomy might affect the development of plaque. Our data support the potential of carotid bifurcation anatomy as a risk factor for the development of atheroma. Longitudinal studies are now required.

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