Sex Differences in Carotid Bifurcation Anatomy and the Distribution of Atherosclerotic Plaque

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Background and Purpose—Plaque formation at arterial bifurcations depends on vessel anatomy, particularly the relative sizes of the branches, and the ratio of the outflow to inflow area. The facts that carotid plaque is more common in men and that carotid bruits in the absence of stenosis are more frequent in women raise the possibility that there are sex differences in carotid bifurcation anatomy. We studied 5395 angiograms from the European Carotid Surgery Trial.

Methods—To minimize secondary changes we excluded angiograms with ≥50% stenosis and also studied vessels with no disease. We measured arterial diameters at disease-free points and calculated the following ratios: internal/common (ICA/CCA); external/common (ECA/CCA); internal/external (ICA/ECA) carotid arteries; carotid bulb/CCA; and outflow/inflow area. We related these to sex and also studied the distribution of plaque in the whole trial population.

Results—Among 2930 angiograms with <50% stenosis, the mean ICA/CCA ratio, ICA/ECA ratio, and outflow/inflow area ratio were larger in women than in men (all \( P < 0.0001 \)). The findings were similar in 622 bifurcations without atheroma. There were also differences in the distribution of plaque, with men more likely to have the maximum stenosis distal to the carotid bulb (odds ratio, 2.29; 95% CI, 1.33 to 4.01; \( P = 0.001 \)) and women more likely to have stenosis of the ECA (odds ratio, 1.54; 95% CI, 1.30 to 1.85; \( P < 0.0001 \)).

Conclusions—Sex differences in carotid bifurcation anatomy are not limited to absolute vessel size. In addition, the outflow to inflow area ratio is bigger in women, and relative to the CCA and ECA, women have larger ICAs than men. Irrespective of whether these differences are congenital or acquired, they may partly explain the sex differences that we found in the distribution of plaque and the sex differences in the prevalence of carotid atheroma in the general population. (Stroke. 2001;32:1525-1531.)

Key Words: anatomy ■ angiography ■ carotid arteries ■ gender

The carotid bifurcation is one of the most common sites of atherosclerotic plaque.\(^1\) Plaque formation is thought to originate from endothelial damage caused by disturbances in local blood flow,\(^2\) which are influenced by bifurcation anatomy.\(^4,5\) Previous studies have suggested that the outflow to inflow area ratio, ie, the ratio of the sum of the cross-sectional areas of the branches divided by the cross-sectional area of the parent vessel, plays an important part in plaque formation.\(^6,7\) The area ratio influences the amount of reflection of a pulse wave arriving at a bifurcation. Low ratios (ie, a relatively small outflow to inflow area) result in loss of flow energy, increasing local stress, and endothelial damage due to increasing reflection of the pulse wave. A study of 6 patients with premature atheromatous disease of the aortic bifurcation reported an association between a small ilioaortic area ratio and the presence of premature atheromatous disease.\(^8\) A small postmortem study found that patients with carotid atheroma tended to have a smaller outflow to inflow area ratio at the carotid bifurcation than patients with no evidence of disease.\(^9\)

If plaque formation is partly determined by bifurcation anatomy, variation in bifurcation anatomy could partly explain differences in the prevalence of carotid plaque. For example, population studies have shown that carotid atheroma is more prevalent in men.\(^10–12\) This is thought to be partly due to differences in sex hormone levels and differences between men and women in the prevalence of other vascular risk factors,\(^13,14\) but sex differences in carotid bifurcation anatomy could also partly account for sex differences in the prevalence of carotid atheroma. However, there has been little investigation of variation in bifurcation anatomy with sex. The only differences described are that men tend to have larger vessels with thicker walls.\(^15,16\) Only one study has examined differences in the relative sizes of the branches of the bifurcation.\(^16\) It included 61 patients (35 men, 26 women) and found no variations of the vessel diameter ratios with sex. However, because of the small number of patients it lacked the statistical power to exclude moderate differences, and it did not examine the outflow to inflow area ratio. To our knowledge there has been no large study of sex differences in carotid bifurcation anatomy.

Our aim was to determine the extent of any sex differences in carotid bifurcation anatomy by reviewing the 5395 angio-

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grams from the 2168 men and 850 women in the European Carotid Surgery Trial (ECST). Given the possible importance of relative vessel sizes in the development of disease, we determined the vessel diameter and area ratios of the main branches of the carotid bifurcation. We also studied sex differences in the distribution of atherosclerotic plaque. The large number of patients provided considerable statistical power. All patients in the trial underwent angiography, permitting accurate measurement of the vessel dimensions. Detailed baseline clinical data were collected on each patient, allowing analysis of other possible influences on vessel anatomy.

Subjects and Methods

We studied the carotid angiograms of patients randomized in the ECST. The methods and results of the 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 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 anatomy. For example, blood pressure and blood flow decrease beyond a stenosis of $\geq 80\%$, and the internal carotid artery narrows distal to a stenosis of $\geq 70\%$. 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 patients with $\geq 50\%$ stenosis of the internal (ICA) or common carotid artery (CCA) (ECST criteria). The reproducibility of this measurement and its equivalence with other methods have been reported previously.

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 sex differences in bifurcation anatomy might be caused by differences between men and women in the acquisition and quality of the angiograms, we compared the following categories between sexes: 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. Use of ratios eliminated the magnification factor of the angiograms and, if we assume that the blood vessel cross sections were approximately circular, produced results that were independent of the projection angle. Use of vessel ratios therefore enabled us to compare nonstandardized angiograms from different centers.

We studied the relative sizes of the CCA, ICA, and external carotid arteries (ECA) and of the carotid bulb. 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). In patients with atheroma, the diameter of the carotid bulb had to be estimated because plaque was most frequently located here and obscured the outline of the vessel wall. Measurements were made by a single observer (P.M.R.) on all available angiograms of symptomatic 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 side was defined as described previously.

Since apparent variation 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 (P.M.R.) measured 1 month apart, and a second independent observer measured the ICA/CCA ratio on a consecutive series of 976 of the study angiograms to determine interobserver agreement.

We calculated the ratios of the diameters of the ICA to CCA, ECA to CCA, and ICA to ECA, the ratio of the carotid bulb to the CCA, and the ratio of the outflow to inflow area, calculated as $(\text{ICA}^2 + \text{ECA}^2)/\text{CCA}^2$. We compared the means of all vessel diameter and area ratios between men and women. In addition, we determined the 10th, 25th, 50th, 75th, and 90th percentiles of the total population distribution for each vessel diameter and area ratio. Using these values as cutoff points, we formed the following categories for each vessel diameter and area ratio: $<10\%$ percentile, 10th to 24th percentile, 25th to 49th percentile, 50th to 74th percentile, 75th to 89th percentile, and $\geq 90\%$ percentile. We calculated the odds of men being in a particular category compared with women. To assess the consistency of the results independently of the severity of atheromatous disease, the analysis was also performed on angiograms with no disease.

The following baseline clinical characteristics were collected in the ECST: age, 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, or minor or major stroke before randomization. To determine a possible association with bifurcation anatomy, we related each variable to the vessel ratios. When a statistically significant relationship (corrected for multiple comparisons) was discovered, we performed multiple regression analysis to further evaluate the association. Some patients had bilateral stenosis $<50\%$, and both their bifurcations were included in the analysis. This would have resulted in double counting of their baseline characteristics. To avoid any potential bias, we therefore analyzed the baseline data both in relation to the patients and in relation to the bifurcations included in the study.

Assessment of the Distribution of Atherosclerotic Plaque

To study the distribution of disease we included angiograms of all 5007 symptomatic bifurcations in our analysis. We measured the degree of stenosis and the total length of the segment of vessel...
affected by plaque. The length of the plaque was recorded as a ratio with the diameter of a disease-free portion of the CCA. We determined the location of the plaque as indicated by point of maximum stenosis. This was classified as being located in the CCA, the bulb of the ICA, or distal to the bulb of the ICA. We also determined the prevalence and extent of disease in the proximal ECA. The degree of stenosis of the ECA was calculated in a manner similar to the ECST method of measurement of ICA stenosis, ie, we used the estimated normal lumen diameter at the point of maximum stenosis as the denominator. We compared each of these assessments between men and women.

Statistical analysis was done with SPSS for Windows version 9.0.

Results

Of the 5395 angiograms, 2930 had carotid stenosis of <50%.

We found that 1420 patients had unilateral ICA or CCA stenosis of <50%, and 755 patients had ICA stenosis of <50% bilaterally. Therefore, we had 2930 bifurcations (2105 male, 825 female) in 2175 patients (1559 male [mean age, 62.1 years; SD 8.2], 616 female [mean age, 62.3 years; SD 8.6]) available for study. The results below are based on 2930 carotid bifurcations. All analyses were also performed in relation to patients and produced virtually identical results (data available from authors). There were no sex differences in the angiographic view, the number of views available, the method of image acquisition, the angiographic technique, or the image quality. Measurements of the ICA/CCA ratio showed good intraobserver reliability. There was no difference, and therefore no bias, between the mean values of the first and second readings, and the measurements were highly correlated ($r=0.85$; 95% CI, 0.78 to 0.90; $P<0.0001$). Interobserver agreement on the 976 independently assessed angiograms was also good. There was no significant difference between the population mean ICA/CCA ratios obtained by the 2 observers, and the measurements were highly correlated ($r=0.87$; 95% CI, 0.78 to 0.84; $P<0.001$).

Arterial Lumen Diameter and Area Ratios

The Table shows the vessel ratios that we determined. The overall mean ICA/CCA ratio was 0.63 (95% CI, 0.62 to 0.64). It was significantly ($P<0.0001$) higher in women (0.67; 95% CI, 0.66 to 0.68) than in men (0.62; 95% CI, 0.61 to 0.63). This difference was also present when the analysis was confined to bifurcations with no disease. Figure 2A shows that low ICA/CCA ratios were more frequent in men and higher ICA/CCA ratios more frequent in women. We did not find a significant difference between men and women in the bulb/CCA ratio (Figure 2B) or in the ECA/CCA ratio (Figure 2C). However, high ICA/ECA ratios were more common in women than in men (Figure 2D), and consequently the mean ICA/ECA ratio was significantly ($P<0.0001$) higher in women (1.19; 95% CI, 1.18 to 1.22) than in men (1.10; 95% CI, 1.09 to 1.11). Figure 3 shows that low outflow to inflow area ratios were more common in men than in women. The mean ratios were 0.71 (95% CI, 0.70 to 0.72) and 0.77 (95% CI, 0.75 to 0.79), respectively. As cutoff points for the categories shown in Figures 2 and 3, we used the 10th, 25th, 50th, 75th, and 90th percentiles of the population distribution for each vessel diameter and area ratio. However, because of digit preference, some values occurred more than once. Therefore, the number of bifurcations in each category did not always correspond exactly with the percentiles. The
The vessel diameter ratios were normally distributed. In a previous study we had therefore defined the lower limit of normal of the ICA/CCA ratio as a ratio 2 SDs below the overall mean value (ie, below the 2.5th percentile). \(^{22}\) The lower limit was 0.42. However, given the systematic difference between men and women, we reevaluated this. Since the mean ICA/CCA ratio (SD) was 0.62 (0.11) in men and 0.67 (0.11) in women, we obtained lower limits of normal of 0.40 and 0.45, respectively.

We related the vessel diameter ratios to the baseline clinical data collected in the ECST. The majority of baseline characteristics were unrelated to bifurcation anatomy. Some variables (smoking, history of peripheral vascular disease, presentation with ocular ischemia) were associated with small differences in the vessel ratios. However, these were all much smaller than the sex effect. The sex differences were independent of all other baseline characteristics in multiple regression analyses.

**Distribution of Atherosclerotic Plaque**

In the whole trial population, the mean stenosis was 51% (SD 22.5). This did not differ significantly between men and women \((P = 0.27)\). However, men were more likely than women to have the point of maximum stenosis distal to the bulb of the ICA \((OR, 2.29; 95\% \text{ CI}, 1.33 \text{ to } 4.01; P = 0.001)\).
There were no sex differences in the length of the stenosis expressed as a ratio with the diameter of a disease-free portion of the CCA: the mean value was 1.98 (95% CI, 1.90 to 2.05) for women and 1.96 (95% CI, 1.91 to 2.00) for men. Atherosclerotic disease in the ECA was more prevalent in women. Women were more likely than men to have plaque in the ECA (OR, 1.54; 95% CI, 1.30 to 1.85; \( P < 0.0001 \)) and were more likely to have stenosis \( \geq 50\% \) (OR, 2.0; 95% CI, 1.56 to 2.57; \( P < 0.0001 \)).

**Discussion**

Our findings show that sex differences in carotid bifurcation anatomy are not limited to the absolute size of vessels. In addition, relative to the ECA and to the CCA, the ICA is larger in women than in men, and in relation to the inflow area, women have larger outflow areas than men (Figure 4). These differences in bifurcation anatomy were independent of other baseline characteristics. We also found sex differences in the distribution of carotid bifurcation plaque. Men were more likely to have the point of maximum stenosis distal to the bulb of the ICA, whereas women were more prone to develop disease of the ECA.

**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 community-based cohorts. Our study was based on a clinical trial population with carotid territory ischemic events. However, the data available in the ECST would have been impossible to obtain in a community-based study because the invasive nature and risks of angiography prohibit its use in healthy subjects. Angiography is a well-established, high-quality method of vascular imaging, and the ECST afforded an opportunity to study carotid anatomy angiographically in a large number of patients. The only previous angiographic study that examined the relative sizes of the carotid bifurcation vessels was too small to show the extent of sex differences in bifurcation anatomy with sufficient statistical power. Second, 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. However, by excluding angiograms with \( \geq 50\% \) stenosis, we minimized such secondary effects. Moreover, our analysis of disease-free, contralateral bifurcations produced very similar results (Table). Third, angiograms were obtained from many different centers. Consequently, projection angles, magnification factors, type of angiography, and image quality were not standardized. All these were potential confounding factors in the comparison of vessel dimensions. However, we did not find any differences in type of angiography, method of image acquisition, film quality, number of views obtained, or other potential angiographic confounders between men and women. Fourth, angiography depicts the vessel lumen rather than the vessel wall. It is therefore possible to miss early atherosclerotic changes, in particular in the carotid bulb, a predilection site for atheroma. This could lead to an underestimation of the true disease-free vessel diameter. However, since overall there were no sex differences in the extent of atheromatous disease in our population, it is unlikely that underestimating the presence of very mild atheroma would have resulted in bias, and it should therefore not have an impact on our findings. Fifth, vessel diameters depend on blood pressure and the force of cardiac contraction. The diameters of the branches of the carotid bifurcation vary, on average, by 4% to 6% between systole and diastole.
However, since we obtained all measurements of a bifurcation from a single film, all the vessels were at the same point of the cardiac cycle. Furthermore, we calculated the vessel diameter ratios, and these do not change significantly with the cardiac cycle. Finally, our study population consisted of older individuals with symptomatic cerebrovascular disease. The anatomy of the carotid bifurcation changes with age independently of any effect of atherosclerosis, and it is possible that some of the anatomic differences we have shown are acquired rather than congenital. Our findings should therefore also be confirmed in younger disease-free populations.

Sex Differences in Bifurcation Anatomy

Our results demonstrate that, when one compares the ICA with the ECA, on average, women tend to have relatively larger ICAs and smaller ECAs than men. This could reflect the fact that women have less skull and facial tissues than men and therefore divert proportionately less blood here and proportionately more to the brain. Sex differences in carotid anatomy could explain the increased occurrence of asymptomatic carotid bruits in women compared with men. Ford et al showed that women with an asymptomatic carotid bruit are up to 5.7 times less likely than men with bruits to have a stenosis of the ICA. These non–disease-related bruits were not related to differences in hematocrit, occurrence of cardiac murmurs, or constitutionally smaller arteries. No explanation for the origin of the bruits was offered by the authors. Our findings raise the possibility that they may be due to anatomic differences. The relatively smaller ECA in women could result in differences in blood flow patterns at the bifurcation and the generation of bruits.

Our findings show that there were small but highly significant differences in some of the mean vessel diameter and area ratios between men and women. In addition, the differences in the number of men and women at the edges of the distribution were large. For example, the odds of having an ICA/CCA ratio 10th percentile were 3.9 times higher in men than in women, and the odds of having an ICA/CCA ratio 90th percentile were twice as high in women than in men. Sex differences were therefore particularly marked at the edges of the distribution, ie, among individuals with small ICA/CCA ratios there was a large excess of men, and among individuals with high ICA/CCA ratios there was a large excess of women. Since our defined cutoff points were the 10th and 90th percentiles, this still included approximately 20% of the trial population, and when the results are extrapolated to the general population, they apply to a large number of individuals.

Localization of Disease

Previous studies have suggested that plaque formation may partly be determined by bifurcation anatomy. In flow models, Karino and Goldsmith pointed out the importance of the diameter ratios at bifurcations and also the presence of sudden vessel expansions, such as the carotid bulb in the formation of flow disturbances, which could then have an impact on plaque formation. Womersley and Gosling et al suggested that the area ratio of an arterial bifurcation, calculated as the sum of the cross-sectional areas of the branch vessels divided by the cross-sectional area of the parent vessel, is of particular importance in the development of plaque. A proportion of a pulse wave arriving at a bifurcation is reflected, setting up a standing wave of pressure proximal to the point of reflection. The higher the degree of reflection, the more hemodynamic stress will develop locally, and more flow energy will be lost. An increase in local pressure can lead to endothelial damage and favor plaque development. Gosling et al calculated that the optimal area ratio of an arterial bifurcation, causing the least reflection of pressure and least loss of flow energy, is 1.15. Any deviation from this ratio in either direction leads to increasing reflection of incoming pulse waves and potentially favors plaque development in the long term. Gosling et al stated that the area ratio of the aortic bifurcation is close to the ideal value in human infants but decreases with age, reaching a value of 0.75 by age 45 years, and thus possibly contributing to atherosclerosis in the elderly. On the basis of these considerations, Spelde et al studied the area ratios of 60 normal and 40 diseased carotid bifurcations at postmortem and found that the area ratio was lower in the diseased bifurcations. However, they did not quantify the extent of disease, and some of the anatomic changes could have been secondary to atheroma.

These studies suggest that differences in bifurcation anatomy might partly account for differences in plaque formation. Population studies show that men have a higher prevalence of carotid atherosclerosis than women, especially before the age of 50 years. This is thought to be partly due to differences in sex hormone levels and differences between men and women in the prevalence of other vascular risk factors. However, sex differences in carotid bifurcation anatomy could also be partly responsible for differences in plaque formation. In our study we not only found differences in bifurcation anatomy between men and women, but we also found differences in the distribution of plaque. Women were more likely than men to have plaque in the ECA, whereas the point of maximum stenosis was located distal to the bulb of the ICA more frequently in men. These differences may have been a consequence of the differences in bifurcation anatomy. However, it is not possible to analyze the effects of bifurcation anatomy on plaque formation in a cross-sectional study.

Implications for Measurement of Carotid Stenosis

Sex differences in the relative sizes of the vessels also have implications for the measurement of stenosis. Several methods for measuring carotid stenosis have been described. They all measure the lumen diameter at the point of maximum stenosis but use different denominators to calculate the percentage of stenosis: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method uses a disease-free portion of the ICA distal to the stenosis; the ECST method uses the estimated normal diameter at the site of the lesion; and the common carotid method uses a disease-free portion of the CCA. Sex differences in relative vessel sizes result in 2 problems. First, since the ICA/CCA ratio is, on average, larger in women than in men, the NASCET method will tend to give a higher degree of stenosis.
in women than in men for a given degree of stenosis by the common carotid method or the ECST method. Although it is possible to convert measurements made by one method to those of another, different conversion formulas should ideally be used for men and women. Second, some patients develop abnormal poststenotic narrowing of the ICA once the degree of stenosis is >70%.22 In this situation, the stenosis can no longer be measured reliably by the NASCET method.90 We previously reported the lower limit of the normal ICA/CCA ratio as 0.42.22 However, our present analysis shows that the ICA/CCA ratio is greater in women. This could lead to poststenotic narrowing being missed in women or overestimated in men if the previous lower limit of normal is applied. It is important to identify patients with poststenotic narrowing because they have a low risk of stroke on medical treatment and do not therefore benefit from carotid endarterectomy.22,21 According to the present study, a lower limit of 0.40 should be applied for men and a lower limit of 0.45 should be applied for women to define the presence of abnormal poststenotic narrowing.

Conclusions

Sex differences in carotid bifurcation anatomy are not limited to the absolute size of vessels. In addition, relative to the ECA and to the CCA, the ICA is larger in women than in men, and in relation to the inflow area, women have a larger outflow area. Bifurcation anatomy has been implicated in the development of plaque, and sex differences in bifurcation anatomy could partly account for the sex differences in the prevalence and distribution of carotid atheroma.

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