The Sex Difference in Manifestations of Carotid Bifurcation Disease


SUMMARY One would think that risk factors for transient ischemic attack (TIA) and asymptomatic carotid bruit (ACB) would be similar. In our referral population and in several previously reported cohort populations, however, men outnumber women among patients with TIA. In contrast, women outnumber men among patients with ACB. We found in two independent populations that women with ACB are up to 5.7 times less likely than men to have carotid stenosis. Thus, women are more prone than men to have ACB, but their bruits much less commonly reflect carotid stenosis. Women are probably predisposed to have carotid bruit even in the absence of carotid stenosis. In our referral population of ACB, this tendency among women for carotid bruit without stenosis does not seem to be related to lower hematocrit, higher prevalence of heart murmur, constitutionally smaller carotid arteries, or differences in pulse rate or body habitus.

TRANSIENT ISCHEMIC ATTACKS (TIAs) are often caused by atherosclerosis of the carotid bifurcation. One would expect risk factors for TIA, asymptomatic carotid bruit (ACB), and asymptomatic carotid stenosis to be similar; however, in our Stroke Registry men outnumber women with TIA while women outnumber men with ACB. This observation prompted us to study our referral population to confirm this "gender gap" and investigate its cause.

Materials and Methods

Three separate, non-overlapping populations of patients were studied. Two were chosen from our Stroke Registry, those with the diagnoses of ACB and TIA. A third population, composed of consecutive patients referred to our outpatient carotid ultrasound lab with the diagnosis of ACB, was employed to confirm findings in the Registry ACB population.

Our Stroke Registry is composed of data on all patients on the neurology inpatient service of the North Carolina Baptist Hospital with confirmed discharge diagnoses of TIA, ACB, subclavian steal syndrome, or transient global amnesia. Patients qualify for the diagnosis of TIA only if their histories conform to criteria defined by the Joint Committee for Stroke Facilities.13 Occasional patients with remote cerebral infarction and recent TIs are included in the category of TIA. The category ACB is used in the Registry to denote a murmur localized over the mid-or-upper common carotid artery in patients without previous, ipsilateral, carotid ischemic symptoms. For this study, patients with ischemic symptoms in the distribution of the contralateral carotid artery or vertebral basilar circulation were also excluded. Patients with radiating heart murmurs, venous hums, and other non-carotid vascular sounds in the neck were not included. Those with
murmurs low in the common carotid artery were included in the category of ACB only if an upper carotid murmur was noted to be louder than the lower one. Coexistent heart murmurs and coexisting orbital, occipital, and supraclavicular bruits were recorded. Other data recorded from ACB referrals to the Registry included age, sex, race, height, weight, weight/height ratio, blood pressure on admission, hematocrit, and histories of smoking, ischemic heart disease, diabetes, and hypertension. Many but not all patients with ACB underwent continuous wave Doppler sonography (76 patients) or cerebral angiography (44 patients). When possible (80 patients), each patient was categorized by the presence or absence of >50% internal carotid stenosis. In patients who underwent both angiography and Doppler testing (40 patients), the results of angiography were given precedence. Continuous wave Doppler was interpreted as showing occlusion when there was no detectable flow. Greater than 50% stenosis was diagnosed when there was a Doppler frequency shift >6 KHz. For statistical analyses, patients were considered to have stenosis if either internal carotid was affected. Occluded internal carotid arteries were coded as stenotic.

The third study population consisted of consecutive outpatients referred specifically for evaluation of ACB to the carotid ultrasound lab between January and November 1984. Each of these patients was questioned by a trained interviewer regarding symptoms of TIA or cerebral infarction, and patients who responded positively were excluded. Blood pressure, pulse, and histories of hypertension, diabetes, peripheral vascular disease, smoking, ischemic heart disease, heart murmur, and "high blood fats" were recorded. Each patient's neck was auscultated, and bruits were characterized as soft, medium, or loud in volume and low, medium, or high in pitch. The location of bruits was described as either early systolic, pansystolic, pansystolic with an early diastolic component, or continuous. Each patient underwent real time carotid ultrasonography using an 8 MHz high resolution Biosonics scanner and direct continuous wave Doppler using a 1050 Dopscan imaging system with 5 MHz transducer. Patients were categorized by the presence or absence of >50% internal carotid stenosis by Doppler using criteria described above.

In ACB patients from both the ultrasound lab and the Registry, logistic regression was used to analyze predictors of internal carotid stenosis. Analysis of variance and chi-square analysis were used to test for differences between males and females in the two ACB populations.

Results

Confirmation of a Gender Gap

From July 1976 to August 1984, 511 patients with TIA and 105 patients with ACB were accessed in the Registry. Of patients with TIA, 284 (56%) were men and 227 (44%) were women. Among 44 subsequent consecutive TIA referrals to the Registry between August and October 1984, the male:female ratio was 25:19 (57% males). This ratio is not statistically different from the male:female ratio observed in the initial 511 TIA referrals (p = 0.99 by chi-square).

Of the 105 ACB referrals to the Registry, 38% were men and 62% were women. The male:female ratio of ACB referrals could not be confirmed in subsequent referrals to the Registry because only three ACB referrals were made during the follow-up period. However, among 86 consecutive ACB referrals to the carotid ultrasound lab between January and November 1984, the male:female ratio was 32:54 (63% females). This ratio is not statistically different from the male:female ratio among ACB referrals to the Registry (p = 0.98 by chi-square).

Sex as a Predictor of Carotid Stenosis in ACB Patients

In view of the male preponderance among TIA referrals vis-a-vis the female preponderance among ACB referrals, we hypothesized that women with ACB are less likely than men to have carotid stenosis. This hypothesis was tested by using logistic regression to analyze predictors of internal carotid stenosis in patients with ACB. ACB referrals to the Registry were analyzed separately from ACB referrals to the carotid ultrasound laboratory. For the analysis of the Registry patients, independent variables tested included age, sex, and past histories of hypertension, ischemic heart disease, diabetes, and smoking. Univariate analysis of Registry ACB patients showed that male sex was the strongest predictor of internal carotid stenosis (p = 0.0004). Seventy-seven percent of men (23 of 30) and 34% of women (17 of 50) with ACB had stenosis. After control of sex, age was the next best predictor (p = 0.0193), with the odds of stenosis increasing by a factor of 1.77 with each succeeding decade. After control for age, the odds of stenosis were 5.7 times greater in males than in females. Ischemic heart disease and smoking were more prevalent among men than women (table 1), but the strong correlation between male sex and stenosis persisted after control for ischemic heart disease, smoking, hypertension, and diabetes. Ischemic heart disease, hypertension, diabetes mellitus, and cigarette smoking each failed to predict stenosis (p > 0.05).

To confirm these findings, a separate analysis for predictors of carotid stenosis was performed among ACB referrals to the carotid ultrasound lab. Independent variables tested in this analysis included age, sex, mean blood pressure on examination, and histories of ischemic heart disease, peripheral vascular disease, hypertension, diabetes, smoking, and "high blood fats."

In ultrasound lab ACB referrals, male sex was again the best predictor of carotid stenosis (p = 0.0039). Seventy-two percent of men (23 of 32) and 39% of women (21 of 54) with ACB had internal carotid stenosis (fig. 1), and the odds of stenosis were 4.0 times greater in men than women. Age did not predict carotid stenosis in univariate analysis (p = 0.1160) or after
TABLE 1 Characteristics of Asymptomatic Carotid Bruit Patients from the Registry*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Males (n = 30)</th>
<th>Females (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD) Number below 45 years of age</td>
<td>64 ± 9.5 years</td>
<td>59 ± 13.3 years</td>
</tr>
<tr>
<td>Weight (mean)</td>
<td>75.4 Kg</td>
<td>63.1 Kg</td>
</tr>
<tr>
<td>Height (mean)</td>
<td>172 cm</td>
<td>163 cm</td>
</tr>
<tr>
<td>Blood pressure (mean)</td>
<td>102.5 mm Hg</td>
<td>100.2 mm Hg</td>
</tr>
<tr>
<td>Hematocrit (mean)</td>
<td>43.4%</td>
<td>39.3%</td>
</tr>
<tr>
<td>Ischemic heart disease*</td>
<td>17 (57%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Smoking†</td>
<td>24 (80%)</td>
<td>28 (58%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (13%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (50%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Heart murmur on examination</td>
<td>12 (43%)</td>
<td>15 (31%)</td>
</tr>
<tr>
<td>Supraclavicular bruit</td>
<td>9 (30%)</td>
<td>18 (38%)</td>
</tr>
</tbody>
</table>

*This table describes only ACB patients who underwent either angiography or carotid Doppler testing. †Significantly different (p < 0.05) between sexes.

control for sex (p = 0.1832). History of smoking was the only variable besides sex which predicted stenosis in univariate analysis (p = 0.0318), but the effect of smoking disappeared after control for sex (p = 0.1685). Though there were significant differences between men and women (table 2) in mean blood pressure on examination (p = 0.0086), and histories of smoking (p = 0.006), ischemic heart disease (p = 0.008), and "high blood fats" (p = 0.049), these differences did not explain the strong correlation between male sex and stenosis.

Female Sex as Risk Factor for Carotid Bruit without Stenosis

Considering the female preponderance of our ACB population and the strong association of male sex with carotid stenosis in ACB, we concluded that females are more likely to have carotid bruit even in the absence of carotid stenosis. We, therefore, studied our data in an effort to explain why females have carotid bruit without stenosis.

The hemodynamics of bruit production are not established, but arterial bruits probably reflect either turbulence or vortex formation in blood flow. Turbulence and vortex formation both increase with increases in cardiac output or decreases in blood viscosity. Blood viscosity is dependent primarily upon hematocrit. We, therefore, analyzed our Registry ACB population to determine whether the prevalence of bruit without stenosis in women might be related to lower hematocrit. Not surprisingly, hematocrit was significantly lower in women than men (p = 0.0001), but hematocrit did not predict the absence or presence of stenosis, and male sex remained a strong predictor of stenosis after control for hematocrit (p = 0.0019).

Unfortunately, we did not measure cardiac output in our ACB patients; but, because cardiac output is dependent on pulse rate, we analyzed the effect of pulse as a predictor of stenosis in our ultrasound lab ACB referrals. Pulse rate did not differ between men and women in this population, and pulse rate did not predict stenosis.

TABLE 2 Characteristics of Patients with Asymptomatic Carotid Bruit from the Ultrasound Lab

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Males (n = 32)</th>
<th>Females (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) Number below 45 years old</td>
<td>67 ± 8.7 years</td>
<td>64 ± 11.4 years</td>
</tr>
<tr>
<td>Blood pressure* (mean)</td>
<td>95.1 mm Hg</td>
<td>103.3 mm Hg</td>
</tr>
<tr>
<td>Pulse</td>
<td>73/min.</td>
<td>75/min.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (48%)</td>
<td>29 (55%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (10%)</td>
<td>12 (23%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>7 (28%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Smoking*</td>
<td>27 (87%)</td>
<td>31 (58%)</td>
</tr>
<tr>
<td>High blood fats*</td>
<td>2 (7%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Ischemic heart disease*</td>
<td>7 (22%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>History of heart murmur</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Significantly different (p < 0.05) between the sexes.
To determine whether carotid bruits without stenosis in women could be related to constitutionally narrow carotid arteries, we studied the carotid real time ultrasound lab ACB referrals. The lumen diameters of the internal and common carotid arteries were measured in segments not affected by atherosclerotic plaque. The common carotid lumen diameters were measured in the most proximal segments demonstrable in the real time scan. Internal carotid lumen diameters were measured in the most distal segments possible. Males had wider internal carotid lumina than females (p = 0.0004). Diameters of the common carotid arteries were not significantly different in men than women (p = 0.1108). Internal carotid and common carotid lumen diameters did not predict stenosis among ACB patients, and the association between male sex and stenosis was not explained by differences between the sexes in luminal diameters.

Some clinicians observe that frail, thin patients are predisposed to bruit without stenosis. Based on this observation, we analyzed the effects of height, weight, and weight/height ratio as predictors of stenosis in ACB referrals to the Registry. Women had lesser weights (p = 0.0001), heights (p = 0.0002), and weight/height ratios (p = 0.0026) than their male counterparts, but these differences between the sexes did not explain the association of male sex with stenosis.

Neurovascular examination of ACB patients offered no clues that carotid bruits in women were caused by radiation of heart murmurs or great vessel sounds. In the ultrasound lab ACB referrals, there were no differences between males and females in the volume, pitch, duration, or location of the carotid bruits (p > 0.1). In the Registry ACB referrals, heart murmurs, supraclavicular bruits, and neck base bruits were no more common than carotid bruits, were no more common in women than in men.

Discussion

Cerebral infarction is often caused by carotid bifurcation atherosclerosis but is also often caused by other factors such as small vessel disease, cardiac embolism, and atherosclerosis at other sites. TIA is more closely linked to carotid bifurcation disease. One would expect similarities in risk factors for TIA, ACB, and asymptomatic carotid stenosis. Among our referrals, however, patients with TIA are predominantly male and patients with ACB are predominantly female.

It is unlikely that this gender gap represents a chance occurrence as it was confirmed in subsequent referral populations of TIA and ACB. It could possibly represent an artifact of referral bias to our Registry or ultrasound lab, but its existence is also supported by several cohort studies. Findings from Evans County, Georgia, Framingham, Massachusetts, and Seal Beach, California confirm the male predominance of TIA prevalence and incidence. Other cohort studies from Olmsted County, Minnesota, and Seal Beach, California, and Evans County, Georgia confirm the female predominance of ACB prevalence. All cohort studies have not reached the same conclusions, but the weight of evidence confirms a gender gap between TIA and ACB.

There are several possible explanations for the existence of this gender gap. One might suspect that men with carotid bifurcation stenosis have more concomitant cerebral atherosclerosis at other sites than women, and are, therefore, prone to develop ischemic cerebral symptoms and be excluded from the diagnostic category "asymptomatic carotid bruit." Though this explanation may account partially for the gender gap between TIA and ACB, analysis of our ACB referral population offers another explanation: women with ACB are much less likely than men to have carotid stenosis.

Cutler felt, on the basis of physical examinations, that cervical bruits were referred from the heart or great vessels more often in women than in men. He did not, however, confirm his suspicions with carotid ultrasonography or cerebral angiography. We could not appreciate differences between men and women in the auscultatory features of ACB. In our patients, there were no differences between men and women in the location, duration, pitch, or volume of ACB. Furthermore, coexistent heart murmurs, supraclavicular bruits, and neck bruit were no more common among women than men. Nonetheless, women with ACB had > 50% internal carotid stenosis much less often than men.

In as much as male gender is a known risk factor for atherosclerosis, many will not be surprised by the observation that carotid stenosis is more common in men with ACB than women. However, we interpret the data as showing, not that carotid stenosis is more common in men than women (though this is perhaps also true) but, that women are predisposed to have carotid bruit in the absence of carotid stenosis. Male gender is probably not a strong risk factor for carotid bifurcation atherosclerosis. In contrast, male gender is an exceedingly powerful predictor of carotid stenosis among patients with ACB, with the odds of carotid stenosis being up to 5.7 times higher in men than women after control for age.

We conclude that ACB is more common in females than in males, despite the fact that TIA is more common in males. Females with ACB are much less likely than males to have carotid stenosis or occlusion. Females are probably prone to have carotid bruit even in the absence of carotid stenosis. We do not know why women tend to have carotid bruit without stenosis more often than men, but it is probably not the result of lower hematocrit, higher prevalence of heart murmur, constitutionally smaller carotid arteries, or differences in pulse rate or body habitus.

Acknowledgments

We wish to thank Drs. David Lefkowitz and John R. Crouse for their helpful comments. Spencer Morrison helped in managing data from patients from the ultrasound lab. Edna Mitchell, Karen Gray, and Kelly Williamson each gave unselfishly of their time for this project.

References

Cerebral arteriography was commonly used for the diagnosis of nontraumatic ICH with an accuracy of 90%. Prior to CT, computed tomography (CT) is the best diagnostic modality for the evaluation of intracerebral hemorrhage (ICH). CT determines both the size and location, as well as suggests the etiology of the ICH. Hayward and O’Reilly claim that, even without clinical information, CT predicts the etiology of nontraumatic ICH with an accuracy of 90%. Prior to CT, cerebral arteriography was commonly used for the evaluation of these patients. However, arteriography failed to differentiate mass effect of a hematoma, from that of cerebral infarction or neoplasm. To predict the diagnostic value of cerebral arteriography for the search of an etiology in 102 patients with nontraumatic intracerebral hemorrhages evaluated between 1980 and 1985, arteriography was diagnostic in 22 of 50 non-hypertensive patients and in only 6 of 47 hypertensive patients. Five patients with a bleeding diathesis had normal arteriography. From the total group, we found 12 saccular aneurysms, 9 arteriovenous malformations, 3 cases of moyamoya and 3 instances of superior sagittal sinus thrombosis. One patient had metastatic choriocarcinoma.

Sites of hemorrhage among all patients with diagnostic arteriograms were: lobar 19, intraventricular 5, thalamic 2, caudate 1, and corpus callosum 1. Lobar hemorrhages in the non-hypertensive group and intraventricular hemorrhages in hypertensive individuals had the highest yield of arteriographic abnormalities. We believe cerebral arteriography is indicated in non-hypertensive patients with lobar hemorrhages. Most hypertensive patients, in particular those with putaminal hemorrhages, do not require arteriography.

The Predicted Value of Arteriography in Nontraumatic Intracerebral Hemorrhage

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SUMMARY We retrospectively assessed the diagnostic value of cerebral arteriography for the search of an etiology in 102 patients with nontraumatic intracerebral hemorrhages evaluated between 1980 and 1985. Arteriography was diagnostic in 22 of 50 non-hypertensive patients and in only 6 of 47 hypertensive patients. Five patients with a bleeding diathesis had normal arteriography. From the total group, we found 12 saccular aneurysms, 9 arteriovenous malformations, 3 cases of moyamoya and 3 instances of superior sagittal sinus thrombosis. One patient had metastatic choriocarcinoma.

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COMPUTED TOMOGRAPHY (CT) is the best diagnostic modality for the evaluation of intracerebral hemorrhage (ICH). CT determines both the size and location, as well as suggests the etiology of the ICH. Hayward and O’Reilly claim that, even without clinical information, CT predicts the etiology of nontraumatic ICH with an accuracy of 90%. Prior to CT, cerebral arteriography was commonly used for the evaluation of these patients. However, arteriography failed to differentiate mass effect of a hematoma, from that of cerebral infarction or neoplasm.

To predict the diagnostic value of cerebral arteriography for the search of an etiology in patients with nontraumatic ICH, identified by CT, we retrospectively reviewed the clinical records, angiography results, and CT examinations of patients with ICH evaluated between 1980 and 1985.

Patients and Methods

Our patient population was selected by reviewing the arteriographic records from the University of Iowa Hospital Neuroradiology Service. Clinical records and CT studies were reviewed to identify risk factors for ICH and determine the precise location of the hematomas. The vast majority of patients had unenhanced CT studies. Patients with head trauma, CT evidence of predominant subarachnoid hemorrhage, or prior histo-
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*Stroke.* 1986;17:877-881
doi: 10.1161/01.STR.17.5.877

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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