Gender Differences in Carotid Stenosis: Are We Overdiagnosing Disease in Women?

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Carotid endarterectomy (CEA) reduces the risk for stroke in selected patients with symptomatic and asymptomatic carotid atherosclerosis.[1–5] Because of its observed benefit and the prevalence of carotid bifurcation atherosclerosis, CEA is the most commonly performed vascular reconstructive procedure. In general, the benefit of CEA is related to the degree of stenosis, although in two national trials of patients with asymptomatic disease, observations of the stenosis-specific benefit did not persist.[4,5]

Carotid arteriography is commonly considered the most reliable method for evaluating carotid atherosclerosis, and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators standardized the method of quantifying the degree of carotid stenosis.[1] Carotid duplex ultrasound scanning compares favorably with arteriography in quantifying carotid atherosclerosis.[6–10] In an effort to reduce the risk for ischemic complications from carotid arteriography, many physicians are using carotid duplex scanning as the definitive diagnostic procedure before CEA.[11–13]

Diagnostic criteria for carotid duplex scanning have been established and accepted as reliable from laboratories accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories with ongoing quality-assurance programs. However, despite efforts to maintain accurate diagnostic criteria that reflect arteriographically demonstrable disease, personal observations were made at a worrisome frequency that carotid duplex scanning resulted in overestimation of disease severity in women, yet false-positive studies were infrequently observed in men. This raised the concern that women may have higher velocities in their carotid arteries than men do for similar amounts of disease, and led to this retrospective analysis of carotid duplex ultrasound scanning versus arteriography stratified by gender. The purpose of this study was to examine whether there were velocity differences based on gender in patients with carotid artery disease and whether different velocity criteria should be used in women than men, especially at clinically relevant thresholds of disease.

Methods

Patients who underwent carotid arteriography and carotid duplex scanning during the 10 years from January 1993 through December 2002 were the basis for this study. Arteriography was performed on average 23 days after the ultrasound examination, with 74% of arteriographic examinations performed within 30 days and 95% performed within 82 days of carotid duplex scanning.

Data from 1,019 carotid bifurcations were available. Entries related to internal carotid occlusion (n = 81) were excluded from the analysis. Comparison was performed on the basis of 938 carotid arteries, 536 from men and 402 from women. Average age at the time of ultrasound scanning was 70 ± 10 years for men and 69 ± 10 years for women.

To eliminate a potential bias and other confounding influences, the single most diseased carotid artery was analyzed in 328 men and 241 women overall and at the disease thresholds of 60% and 70% diameter reduction stenoses.

Biplane or triplane contrast arteriography was performed according to patient indication and practice patterns of the attending physicians. The radiologist's interpretation of internal carotid artery (ICA) stenosis was entered into the database. This interpretation was based on the selection of the arteriographic image with the minimal residual lumen compared with the normal diameter of the ICA distal to the lesion, and the percent stenosis calculated. The radiologist's interpretations were validated by independent second measurements as previously reported.[14]

Analyses were made in 536 male and 402 female carotid arteries. Additionally, the single most diseased artery per patient was analyzed by gender. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were averaged for data subsets according to 10% intervals of ICA stenoses. Velocities for each interval were compared between men and women by t-test.

Results

For all intervals, PSV and EDV averaged 9% and 6% higher in women than in men. Significant gender differences existed between PSV and EDV for 60% and 70% stenoses. For 70% stenosis, PSV averaged 285 ± 16 cm/s in women and 236 ± 11 cm/s in men ($p = .01$) and EDV averaged 79 ± 7 cm/s in women and 77 ± 6 cm/s in men ($p = .03$). For 60% stenosis, PSV averaged 228 ± 14 cm/s in women and 189 ± 11 cm/s in men ($p = .03$) and EDV averaged 68 ± 6 cm/s in women and 51 ± 4 cm/s in men ($p = .01$). When a single vessel per patient was analyzed, these observations persisted but lost significance for PSV at 60% stenosis ($p = .18$).

Discussion

Anecdotal observations that commonly accepted velocity criteria overestimate carotid stenosis in women based on arteriographic findings led to this large retrospective analysis. Although this study was retrospective, arteriograms were obtained and interpreted with standardized NASCET criteria and compared with carotid duplex ultrasound scans. Arteriograms and noninvasive studies were interpreted independent of each other. The data appear robust and the observations that women have higher flow velocity in their carotid system, associated with lesser degrees of stenosis, is in keeping with other available information. Two important questions surface: Are there reasonable explanations for this observation? Are these observations clinically meaningful? The answer to both of these questions appears to be "yes."

Women with asymptomatic disease are more prone to have cervical bruits than men. Furthermore, women with cervical bruits are 5.7 times less likely than men to have associated carotid stenosis.[15] Williams and Nicolaides showed that the diameter of the common carotid arteries (CCA), ICA, and external carotid arteries (ECA) were significantly smaller in women compared with those in men.16 Scheel and colleagues confirmed reduced luminal diameters in the carotid circulation in women compared with men.[17]

The differences in size of the ICA and CCA translate into differences in the ICA-to-CCA ratio between genders. There is an interesting difference in the distribution of atherosclerotic plaque that appears to be gender-specific. Schultz and Rothwell reviewed 5,395 arteriograms from the European Carotid Surgery Trial and compared diameter ratios of the ICA, CCA, and ECA with minimal disease to obtain a truer relationship between vessels.[18] Among the 2,930 arteriograms available for review, the mean ICA-to-CCA, ICA-to-ECA, and outflow-to-inflow area ratios were larger in women than in men ($p < .0001$). In addition, there were differences in the distribution of carotid plaque, with men more likely to have maximal stenosis in the ICA and women having a greater degree of plaque within the carotid bulb. Furthermore, women were more likely to have severe disease in the ECA, which would also bias the distribution of existing flow velocity through the patent ICA. A gender-based analysis of carotid plaque distribution was not performed as part of this study.

Changes in arterial wall compliance have also been demonstrated in women, who exhibit increased age-related stiffness of their arteries and develop a higher degree of pulsatility (pulse pressure),[19,20] which predisposes them to a higher velocity for any given blood pressure.

Anemia artifactually increases arterial velocity.[20,21] Women have a relative anemia compared with men, which is also likely to play a role in the velocity differences between genders.

Few physicians will argue that all patients with focal cerebral ischemia ipsilateral to a high-grade carotid stenosis should undergo CEA. The asymptomatic carotid trials that demonstrated benefit have led to an increasing number of asymptomatic patients undergoing treatment for carotid atherosclerosis, both with CEA and carotid angioplasty and stenting. However, women are underrepresented in trials of CEA that have demonstrated superiority to best nonoperative care. Furthermore, the natural history of carotid atherosclerosis appears to be different in women compared with men. At any age, the risk for stroke is greater in men than women.[22] The risk for stroke is higher in men with similar degrees of carotid stenosis,[1,2,4] which may be related to the fact that men have biologically higher-risk lesions. Joakimsen and colleagues showed that atherosclerotic lesions in men were more heterogeneous.[23] These ultrasound characteristics are consistent with plaques that are soft and lipid rich, and are likely to have more intraplaque hemorrhage. These characteristics are associated with an increased risk for ischemic events, including myocardial infarction and stroke.[24,25]

The large trials of CEA emphasize that procedural benefit is predominantly determined by the incidence of operative complications. Additional analyses of the NASCET and ACAS studies suggest that CEA may not be as efficacious in women as it is in men. In the ACAS study, the stroke and death rate at 5 years was reduced by only 17% in women, compared with a 66% reduction in men. In part, this discrepancy was due to a greater incidence of perioperative complications in women (3.6%) than in men (1.7%). Lane and colleagues reported similar observations.[26] They also demonstrated that women had a threefold increase in operative stroke. Other investigators demonstrated higher perioperative risk in women compared with men and a higher incidence of carotid restenosis.[27,28]

There are anatomic, physiologic, and pathologic gender differences that explain the higher-velocity profiles observed in women compared with men. Inasmuch as the natural risk for carotid atherosclerosis is lower in women and the risk for intervention is higher, the threshold for intervention in women should reasonably be higher than the threshold for intervention in men. This is especially true in patients with asymptomatic disease.

In light of the information reviewed above, noninvasive velocity criteria should be adjusted in women to more accurately reflect the underlying disease and to offer a better fit with their risk for carotid atherosclerosis as well as the risks and benefits of intervention.

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