Progression of moderate-to-severe carotid disease

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Objective: Our goals were to investigate the degree to which patient demographics, risk factors, laboratory data, and medications influence moderate carotid disease progression among patients with asymptomatic moderate carotid disease and whether such associations are solely based on how progression is defined. In addition, we aimed to establish optimal threshold criteria to categorize patients at high risk of progression.

Methods: In this retrospective study, 621 arteries were evaluated for internal carotid artery (ICA) stenosis between January 1997 and January 2014 and were determined to have moderate (50%-79%) stenosis via color duplex ultrasonography. “Moderate stenosis” was defined as an ICA peak systolic velocity (PSV) ≥120 cm/s and a diastolic ICA velocity <140 cm/s. Kaplan-Meier analysis of the time to progression was conducted using three independent end points: PSV ≥230 cm/s (liberal criterion); ICA/common carotid artery (CCA) ratio ≥4.0 (moderate criterion), and diastolic ICA velocity ≥140 cm/s (strict criterion). Kaplan-Meier survival curves were generated, and multivariate analysis was performed using Cox regression models. Risk stratification criteria were based on optimal sensitivity and specificity generated from receiver operating characteristic (ROC) curve analysis.

Results: The overall rate of progression was 28.5%, 21.1%, or 5.1% of study-eligible arteries over 5 years using liberal, moderate, or strict criterion, respectively. Using liberal criterion, multivariate analysis suggested that initial PSV ≥200 cm/s, ICA/CCA ratio ≥3, and male gender were significantly associated with progression. Using the moderate criterion, multivariate analysis revealed that initial PSV ≥200 cm/s, ICA/CCA ratio ≥3, and age, and male gender were significantly associated with progression. Using the strict criterion, multivariate analysis revealed that initial PSV ≥200 cm/s was the only statistically significant predictor of progression. No additional patient demographics, comorbidities, initial laboratory values, or medications consistently influenced disease progression across any criteria in our study. ROC analysis suggests PSV ≥165 cm/s is an ideal threshold value for the categorization of high risk patients, as this resulted in an optimal screening sensitivity of nearly 91% and a specificity of 59% over 2 years.

Conclusions: The timing and incidence of carotid disease progression depends on the definition of disease progression. Among all three criteria, only severity of disease at initial presentation reliably predicted progression. Based on the results of our ROC curve analysis, we propose that an initial ICA PSV ≥165 cm/s (sensitivity: 90.7%, specificity: 58.7%) represents a reasonable value for defining high progression risk over a 2-year interval. (J Vasc Surg 2016;63:1505-10.)

Symptomatic patients with moderate (50%-79%) and severe (80%-99%) carotid disease benefit when carotid endarterectomy is added to best medical management.1,3 However, the optimal management of patients with asymptomatic moderate carotid artery stenosis (AMCAS) remains highly controversial.

Disease progression, which is estimated to occur in 15.5% to 25.2% of patients with AMCAS over 2 years of follow-up,6,8 is clearly a risk factor for stroke, transient ischemic attacks (TIAs), and carotid occlusion. Roedder et al10 found that among asymptomatic patients initially presenting with <80% stenosis and a midcervical carotid bruit, progression was associated with an increased incidence of stroke, TIA, and progression to complete occlusion. In addition, 29% of patients who progressed from AMCAS to severe stenosis within 6 months of the start of the study reported having a TIA during this time interval. However, among patients whose plaques remained stable, none experienced a TIA.10 Given the risks associated with disease progression, it would be reasonable for surgeons to follow patients with AMCAS with serial studies and to intervene once progression is identified. However, appropriate follow-up protocols remain ill-defined, and this may be attributable to the widely varying conclusions regarding the incidence, timing, and correlates of plaque progression.

The purposes of this study were to determine the incidence, timing, and predictors of carotid plaque progression in a large cohort of asymptomatic patients initially...
presenting with 50% to 79% stenosis and followed with serial duplex ultrasound studies. To evaluate the influence of the definition of disease progression, we compared our results using liberal, moderate, and strict velocity thresholds. We performed this study with hopes of identifying predictors of progression that would allow for the design of evidence-based duplex follow-up protocols for patients presenting with moderate carotid disease.

**METHODS**

Our objectives were to (1) determine the incidence and timing of disease progression in patients with AMCAS; (2) elucidate predictors of progression; and (3) establish optimal threshold criteria to categorize patients who are at the highest risk of progression.

Between January 1997 and January 2014, 621 internal carotid arteries in 507 asymptomatic patients evaluated by duplex ultrasound at Tufts Medical Center were found to be 50%-79% stenotic using modified Strandness criteria, defined as internal carotid artery (ICA) peak systolic velocity (PSV) ≥120 cm/s and ICA end-diastolic velocity (EDV) <140 cm/s. Arteries were ineligible for inclusion if they had undergone previous surgical intervention, nonatherosclerotic carotid stenosis, or if no subsequent follow-up studies were performed. All ultrasound studies were performed by certified ultrasound technologists and interpreted by staff vascular surgeons following Intersocietal Accreditation Commission guidelines.

Patient demographics (age at initial study, gender, race; comorbidities [hypertension, hypercholesterolemia, diabetes mellitus, smoking history]; laboratory data [glycosylated hemoglobin, total cholesterol, high density lipoprotein, low density lipoprotein]; and medications [warfarin, angiotensin-converting enzyme inhibitors, statins, clopidogrel, ezetimibe, aspirin, and ß-blockers]) were obtained from medical records relevant to the date of the initial study or imaging studies. The end point assessed was progression of disease using the Society of Radiologists in Ultrasound Consensus Conference criterion, based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% ICA stenosis; or (3) EDV ≥140 cm/s (strict criterion), based on modified Strandness criteria. Arteries that met end point criteria at the initial study were excluded from that respective analysis.

Before starting this study, approval was obtained by the Institutional Review Board at Tufts Medical Center. Patient consent was not required because the retrospective nature of this study posed no more than minimal risk to participants.

**Statistical methods.** Descriptive statistics of the patient characteristics corresponding to the initial carotid duplex ultrasound study are presented using means and standard deviations for continuous variables and frequencies and percentages for categoric characteristics. We describe 5-year progression to severe stenosis for artery studied using Kaplan-Meier analyses. The unit of analysis for the study is each individual artery that met inclusion criteria.

Differences in progression risk among patients with various risk factors were examined by analyzing baseline patient data using multivariate Cox regression models. Robust sandwich covariance estimates were used to account for nonindependence of arteries within patients.

Initial covariate selection was performed with a series of unadjusted regression models to identify covariates with $P$ values of <.2. To reduce bias because of the effect of missing data, we imputed missing values for covariates using multiple imputation methods to generate 10 complete datasets. Regression estimates from all 10 imputed datasets were combined using the SAS procedure MIANALYZE (SAS Institute Inc, Cary, NC). Cox proportional hazards regression models were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of progression across baseline severity groups. Key risk factors were compared via stratified Kaplan-Meier survival curves and log-rank tests. To facilitate the interpretation of Cox regression models and Kaplan-Meier analyses, PSV and ICA/CCA ratio were analyzed as binary variables, with 200 cm/s and three, respectively, arbitrarily chosen as cut points; EDV was analyzed in both models as a continuous variable.

To establish an optimal threshold criterion to categorize patients who are at the highest risk of disease progression, a receiver operating characteristic (ROC) curve was generated plotting sensitivity and specificity as a function of PSV, EDV, and ICA/CCA ratio at both 2 years and 5 years of follow-up using the strict criterion.

All statistical analyses were performed using SAS (v 9.3; SAS Institute Inc). Statistical significance was determined using two-sided $P$ values of <.05.

**RESULTS**

Our primary cohort consisted of 621 eligible arteries from 507 patients. The mean follow-up time was 40 months. Demographic characteristics, comorbid conditions, baseline laboratory results, and medication data for those with and without disease progression are described in Table I. Among the initial cohort, the mean age at time of initial presentation was 69.4 ± 9.1 years, 53.3% were male, and 89.5% were Caucasian.

Disease progression using the “liberal criterion”. When the liberal criterion was used, the incidence of progression was 28.5% over 5 years (Fig 1). Results from the unadjusted analyses revealed that an initial PSV ≥200 cm/s, EDV as a continuous variable, and ICA/CCA ratio ≥3 were each independent significant predictors of disease progression (Table II). Cox proportional hazards regression analysis results using multiple imputed data sets

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