Associations of Risk Factors With Segment-Specific Intimal-Medial Thickness of the Extracranial Carotid Artery

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Stroke. 1999;30:1047-1055
doi: 10.1161/01.STR.30.5.1047
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Associations of Risk Factors With Segment-Specific Intimal-Medial Thickness of the Extracranial Carotid Artery

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Background and Purpose—It is generally assumed that risk factors affect extracranial carotid intimal-medial thickness similarly among all arterial segments. This assumption underlies use of single segments or walls of segments as outcome variables for risk factor studies and clinical trials. However, if the impact of risk factors was unequal for various segments or circumferentially asymmetrical within segments, then inferences drawn from a single segment or wall might not be generalizable; furthermore, since individual segments and walls have unique histological characteristics and are differentially exposed to turbulent flow, risk factor relationships with a particular segment or wall may provide inferences regarding pathogenesis of atherosclerosis.

Methods—We evaluated associations of risk factors with intimal-medial thickness at the near and far walls of the common carotid artery, bifurcation, and internal carotid artery in 280 individuals older than 45 years equally divided between coronary artery disease cases and controls and between men and women.

Results—The patterns of differences in mean intimal-medial thickness among segments vary, depending on age, history of hypertension, body mass index in women, and coronary (case-control) status. The asymmetry of disease depended on blood glucose concentrations, prior history of diabetes, smoking, and coronary status. Sex, postmenopausal status, LDL cholesterol, systolic blood pressure, and history of myocardial infarction all had statistically significant relationships with intimal-medial thickness that were fairly homogeneous among arterial sites.

Conclusions—Focus on an individual segments or walls of the extracranial carotid arteries may lead to overestimation or underestimation of associations of risk factors with extracranial carotid intimal-medial thickness. **(*Stroke*. 1999;30:1047-1055.)**

Key Words: atherosclerosis ■ carotid arteries ■ coronary artery disease ■ risk factors ■ ultrasonography

We have previously quantified associations of traditional risk factors with a summary index of extracranial atherosclerosis defined as the aggregate (sum) of intimal-medial thicknesses (IMTs) derived from 12 sites of the extracranial carotid arteries (extracranial carotid IMT) in patients with and without coronary artery disease (CAD).[1] Subsequently, several investigators have evaluated associations of risk factors with other aggregate indices, such as average IMT, or with numbers of plaques (reviewed, eg, in References 2 and 3). In general, investigators have computed these aggregate indices from IMT measured at the near and far walls of the common carotid artery, bifurcation, and internal carotid artery, combining information from the left and right sides (eg, Reference 4), or else they have restricted measurements to the far wall of the common carotid artery (eg, Reference 5). Restricting measurement to the common segment has been justified by the greater reliability of IMT measurements from this site and, conversely, the difficulty in obtaining measurements from the internal carotid and the bifurcation in some populations.[6] However, protocols that involve additional segments have several advantages. First, plaques are most often found in the bifurcation and the internal carotid artery. Thus, including these sites may provide the most sensitive and statistically powerful assessment of disease and disease progression. Second, aggregating data across segments may provide measures that are less sensitive to measurement error; data from the Asymptomatic Carotid Artery Progression Study (ACAPS) indicate that averaging across greater numbers of walls increases the stability of the measure.[7] Finally, restricted protocols carry the implicit assumption that risk factors affect walls and segments in a homogeneous fashion. However, it is conceivable that certain risk factors might have different associations with different segments (or near or far walls) of the extracranial carotid artery. In particular, stronger associations of risk factors with IMT of the bifurcation and internal carotid artery compared with associations with the

Received November 9, 1998; final revision received January 26, 1999; accepted February 18, 1999.

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IMT of the common carotid artery may be hypothesized on the basis of the greater turbulence of flow identified at those sites. If the associations with IMT of the bifurcation or internal carotid were stronger than with IMT of the common carotid artery, then focus on the common carotid may underestimate the importance of such risk factors. Alternatively, it is possible that certain risk factors might relate more strongly to eccentric atherosclerosis involving far walls more than near walls or vice versa. In the former case, estimates based on far walls alone might overestimate the true strength of association. Finally, certain risk factors might affect all segments and both walls of the extracranial arteries in a uniform fashion (homogeneous atherosclerosis). Observance of different associations of individual risk factors with various segments or walls may enlarge our understanding of the pathophysiology of vascular disease.

The purpose of this communication is to evaluate risk factors for their potential to affect differentially one or the other segments or walls of the extracranial carotid arteries in a population of patients that has been well characterized for its coronary status.

Subjects and Methods

Population

The population recruited for this study has been described previously and was drawn from individuals who underwent cardiac catheterization at the Wake Forest University School of Medicine to define the status of coronary atherosclerosis.[8,9] Inclusion criteria included age ≥45 years and catheterization that identifies cases (≥50% stenosis of 1 or more vessels) and controls (no lumen irregularities). Equal numbers of cases, controls, men, and women were recruited according to a stratified random sampling strategy. Patients with coronary stenosis of <50% were excluded ("nonobstructive" coronary disease). Exclusion criteria included clinical instability (patients with myocardial infarction within the last 6 weeks, cardiogenic shock, or other evidence of clinical instability), previous coronary bypass surgery or angioplasty, use of certain medications, or presence of certain clinical conditions that would alter plasma lipids (use of hypolipidemic drugs, thyroid medication, cortisone; liver disease; alcohol abuse; creatinine ≥2.5; presence of cancer). In addition, patients with history of carotid endarterectomy were excluded. Participants all provided informed consent.

Clinical Evaluation

Trained interviewers collected pertinent medical history and risk factor profiles from all participants at a preventive cardiology outpatient clinic within 6 to 8 weeks after catheterization. These included heart and vascular disease history, vascular disease risk factor status, menstrual status, medication use, and prior diagnostic evaluations. Clinic coordinators also measured height, weight, and blood pressure. Blood was drawn for laboratory analyses. The presence of hypertension was defined by history of the disease, a systolic blood pressure >150 mm Hg, or a diastolic blood pressure >90 mm Hg. The presence of diabetes was defined by history of the disease or by a fasting glucose level of >140 mg/dL. Smoking status was recorded as the number of pack-years smoked.

Lipoprotein Analysis

Plasma total cholesterol and triglyceride concentrations as well as lipoprotein cholesterol concentrations were quantified in the Centers for Disease Control and Prevention–standardized Lipid Laboratory of the Wake Forest University School of Medicine according to the Lipid Research Clinics Program.[9] Cholesterol and triglyceride determinations were performed on the Technicon RA-1000 with the use of enzymatic methods. The heparin-manganese precipitation procedure described in the Lipid Research Clinics manual was used to isolate plasma HDL for assay of its cholesterol concentration. For the HDL cholesterol assay, the RA-1000 enzymatic method was used with the substitution of the Technicon reagent by the Boehringer-Mannheim high-performance cholesterol reagent. HDL and LDL cholesterol were recovered after ultracentrifugation (in the 1.006 infranatant), and LDL was quantified as the difference between the 1.006 infranatant cholesterol and the cholesterol in the infranatant after precipitation of LDL.

Ultrasound

The ultrasound methodology for this study has been previously described.[8,9] A Biosound 2000 II s.a. high-resolution ultrasound unit equipped with an 8-MHz transducer was used. Images were transcribed on a super VHS one-half-inch videotape. A RMI 414B tissue-mimicking phantom was used to monitor and ensure instrument performance. Sonography and reading were accomplished by trained and certified sonographers and ultrasound readers with regular quality control. Patients were examined in the supine position; each carotid wall and segment was interrogated independently from continuous angles to identify the thickest intima-media site. Each scan of the common carotid artery began just above the clavicle, and the transducer was moved cephalad through the bifurcation and along the internal carotid artery. Three segments were identified on each side: the distal 1.0 cm of the common carotid proximal to the bifurcation, the bifurcation itself, and the proximal 1.0 cm of the internal carotid artery. At each of the 3 segments for both the near and far walls in the left and right carotid artery, the sonographer identified 2 interfaces: on the near wall the first interface (interface 2) is the adventitial-medial boundary, and the second (interface 3) is the intima-lumen boundary; on the far wall the first interface (interface 4) is the lumen-intima, and the second (interface 5) is the media-adventitia. Thus, 2 to 3 and 4 to 5 define IMT on the near and far walls, respectively. When these interfaces were (separately) demonstrated, the sonographer reduced gain and time gain control setting as low as possible to decrease artifact and then recorded the video images that included the maximum 2 to 3 and 4 to 5 IMT at each of the 12 segments. The sonographer focused on the near and far walls separately (multiple focus zones). Readers examined the videotapes and identified frames that demonstrated the maximum 2 to 3 and 4 to 5 IMT within each segment. Frames were captured electronically and displayed on high-resolution monitors, and maximum IMT was calculated at each of the 12 sites (near and far walls of the common carotid, bifurcation, and internal carotid on the left and right sides). The mean absolute difference in replicate measurements of the internal carotid artery with the use of this protocol was 0.11 mm.

Statistical Analysis

Laird-Ware models for clustered data[10] were fitted to the IMT data with the use of maximum likelihood[11] to compute segment-, wall-, and side-specific means and pooled SEs. This approach, rather than calculating raw means, provides some protection against biases associated with nonvisualization[12,13] and appropriately addresses intersite correlations. Comparisons among means from different segments, walls, or sides were made with Wald tests.[11] The consistency of segment differences between the near and far walls was assessed by incorporating an interaction term in these models. Similar approaches were used to assess relationships between predictors and IMT for subgroups of sites and to assess the consistency of these relationships among these subgroups. These analyses were performed for all participants and separately for cases and controls.

Results

A partial roster of demographic features and risk factor data for male and female cases and controls has been reported previously.[8,9] A full enumeration of those data is presented in Table 1. By design, equal numbers of male and female cases

TABLE 1. Baseline Characteristics of the Study Cohort

Baseline Characteristic	All Participants (n=280)	Cases Only (n=141)	Controls Only (n=139)	P* (Cases vs Controls)
Female, %	50.0	49.6	50.4	0.91
Black, %	8.6	4.3	12.9	0.009
Age, y	59±9	62±8	56±8	<0.001
Systolic blood pressure, mm Hg	132±19	135±19	128±19	0.001
Diastolic blood pressure, mm Hg	78±10	77±11	78±10	0.40
Hypertension, %	51.4	58.2	44.6	0.02
Smoking, pack-years	22±39	25±32	18±26	0.04
Current smoking, %	25.7	27.0	24.5	0.63
Glucose, mg/dL	115±47	126±57	103±32	<0.0001
Diabetes, %	22.5	29.8	15.1	0.003
Total cholesterol, mg/dL	212±39	217±39	207±39	0.04
Triglycerides, mg/dL	156±86	164±79	143±88	0.04
LDL cholesterol, mg/dL	135±33	141±32	130±33	0.008
HDL cholesterol, mg/dL	45±14	43±12	47±16	0.02
BMI, kg/m^2				
Women	27.3±6.2	26.5±5.6	28.0±6.7	0.17
Men	26.7±3.7	26.4±3.1	26.9±4.2	0.45
Prior MI, %	21.8	34.0	9.4	0.001

Values are mean±SD or percentage.
*t test for continuous characteristics; χ^2 test for discrete characteristics.

and controls were recruited. Cases were older and more likely to be diabetic, hypertensive, smoke cigarettes, and have higher plasma concentrations of total and LDL cholesterol and lower concentrations of HDL cholesterol.

Table 2 presents the mean maximum extracranial carotid IMT by site for the 12 sites visualized in cases and controls in this study and for the group as a whole. Analyses revealed statistically significant differences among segments (greatest at the bifurcation and least at the common; $P<0.0001$) and between the near and far walls (far walls thicker; $P<0.0001$). No statistically significant differences were observed between the left and the right sides (providing rationale for pooling these data). There was a statistically significant interaction between walls and segments ($P<0.0001$): the difference between near and far walls was greatest at the bifurcation and least at the common ($P<0.0001$). These differences held not only for the group as a whole but also for the cases ($P<0.001$) and controls ($P=0.002$) separately.

Tables 3 and 4 summarize relationships between risk factors and IMT of individual segments, individual walls, and all sites combined. Also included is the level of statistical significance for heterogeneity of these relationships among individual segments or between near and far walls. Although statistically significant associations of risk factors with seg-

TABLE 2. Descriptive Statistics for IMT Measures by Segment and Wall

		All Participants (n=280)		Cases Only (n=141)		Controls Only (n=139)	
Segment	Wall	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Common	Far	1.01±0.39	0.98±0.35	1.14±0.48	1.05±0.45	0.89±0.20	0.90±0.18
	Near	0.94±0.26	0.94±0.32	1.00±0.30	0.97±0.32	0.88±0.20	0.91±0.22
Bifurcation	Far	1.70±0.92	1.68±0.89	1.99±1.03	1.97±0.99	1.41±0.67	1.39±0.64
	Near	1.49±0.75	1.38±0.66	1.73±0.87	1.58±0.70	1.25±0.51	1.19±0.55
Internal	Far	1.20±0.74	1.33±0.88	1.36±0.79	1.59±0.98	1.06±0.66	1.06±0.66
	Near	1.07±0.59	1.08±0.61	1.29±0.71	1.20±0.73	0.84±0.27	0.97±0.42
Inference (P)							
Differences among segments		<0.0001		<0.0001		<0.0001	
Differences between walls		<0.0001		<0.0001		<0.0001	
Differences between sides		0.21		0.26		0.19	
Segment by wall interaction		<0.0001		0.002		<0.0001	

TABLE 3. Relationships Between IMT and Continuous Predictors

Continuous Predictor	Common Segments	Bifurcation Segments	Internal Segments	Near Walls	Far Walls	All Sites	Differences Among Segments (*P*)	Differences Between Walls (*P*)
All participants								
Age, μm/y	10.00±1.48 (*P*<0.0001)	25.00±3.69 (*P*<0.0001)	17.71±3.22 (*P*<0.0001)	8.98±1.55 (*P*<0.0001)	11.77±2.04 (*P*<0.0001)	8.37±1.41 (*P*<0.0001)	<0.0001	0.21
Blood pressure, μm/mm Hg								
Systolic	2.10±0.74 (*P*=0.005)	5.79±1.83 (*P*=0.002)	4.56±1.60 (*P*=0.004)	1.66±0.77 (*P*=0.03)	3.10±0.99 (*P*=0.002)	1.74±0.69 (*P*=0.01)	0.14	0.07
Diastolic	−1.12±1.38 (*P*=0.42)	−3.18±3.43 (*P*=0.35)	2.01±3.08 (*P*=0.51)	−0.57±1.44 (*P*=0.69)	−0.65±1.84 (*P*=0.73)	−0.30±1.30 (*P*=0.82)	0.19	0.61
Smoking, μm/pack-years	1.59±0.47 (*P*=0.008)	3.46±1.17 (*P*=0.004)	2.85±1.02 *P*=0.006)	1.59±0.57 (*P*=0.006)	3.73±0.69 (*P*<0.0001)	2.25±0.49 (*P*<0.0001)	0.18	0.01
Glucose, μm/mg/dL	0.79±0.29 (*P*=0.006)	1.65±0.72 (*P*=0.02)	1.47±0.64 (*P*=0.02)	0.49±0.30 (*P*=0.11)	1.57±0.38 (*P*<0.0001)	0.69±0.27 (*P*=0.01)	0.82	0.002
Lipids, μm/mg/dL								
Total cholesterol	0.46±0.35 (*P*=0.20)	0.13±0.88 (*P*=0.88)	−0.11±0.76 (*P*=0.89)	0.28±0.36 (*P*=0.44)	0.59±0.47 (*P*=0.21)	0.20±0.33 (*P*=0.55)	0.75	0.18
HDL cholesterol	−1.00±0.97 (*P*=0.30)	−2.66±2.45 (*P*=0.28)	−3.10±2.09 (*P*=0.14)	−1.29±0.99 (*P*=0.20)	−0.69±1.30 (*P*=0.60)	−1.07±0.91 (*P*=0.24)	0.36	0.72
LDL cholesterol	0.83±0.41 (*P*=0.05)	0.94±1.04 (*P*=0.44)	0.16±0.91 (*P*=0.86)	0.68±0.43 (*P*=0.11)	0.76±0.56 (*P*=0.17)	0.50±0.39 (*P*=0.20)	0.81	0.43
Triglycerides	−0.06±0.11 (*P*=0.55)	−0.21±0.26 (*P*=0.44)	0.00±0.22 (*P*=0.97)	−0.09±0.11 (*P*=0.41)	0.08±0.14 (*P*=0.58)	−0.04±0.10 (*P*=0.68)	0.62	0.16
BMI, μm/kg/m^2								
Women	−2.74±3.12 (*P*=0.38)	−14.80±7.59 (*P*=0.05)	0.95±6.95 (*P*=0.89)	−2.60±3.15 (*P*=0.41)	−3.51±4.21 (*P*=0.41)	−3.03±2.88 (*P*=0.29)	0.05	0.91
Men	−1.12±5.38 (*P*=0.83)	−7.79±13.62 (*P*=0.57)	−0.84±11.53 (*P*=0.94)	0.78±5.84 (*P*=0.89)	−1.78±6.91 (*P*=0.80)	2.39±4.98 (*P*=0.63)	0.87	0.58
Cases only								
Age, μm/y	8.61±2.55 (*P*=0.001)	26.00±6.07 (*P*<0.0001)	17.36±5.00 (*P*=0.003)	6.77±2.55 (*P*=0.009)	7.34±3.79 (*P*=0.0006)	7.23±2.42 (*P*=0.003)	0.01	0.14
Blood pressure, μm/mm Hg								
Systolic	1.99±1.13 (*P*=0.08)	5.15±2.76 (*P*=0.06)	4.58±2.58 (*P*=0.08)	1.66±1.11 (*P*=0.14)	3.77±1.69 (*P*=0.03)	1.76±1.06 (*P*=0.03)	0.45	0.12
Diastolic	0.30±2.05 (*P*=0.88)	−1.03±4.98 (*P*=0.84)	2.88±4.74 (*P*=0.54)	1.65±2.02 (*P*=0.42)	0.35±3.04 (*P*=0.91)	1.69±1.93 (*P*=0.38)	0.57	0.89
Smoking, μm/pack-years	1.84±0.71 (*P*=0.01)	3.88±1.83 (*P*=0.04)	3.85±1.63 (*P*=0.02)	1.19±0.74 (*P*=0.11)	4.47±1.04 (*P*<0.0001)	1.91±1.04 (*P*<0.0001)	0.64	0.008
Glucose, μm/mg/dL	0.23±0.38 (*P*=0.55)	0.02±0.92 (*P*=0.99)	0.01±0.86 (*P*=0.99)	0.01±0.38 (*P*=0.97)	1.26±0.56 (*P*=0.02)	0.28±0.36 (*P*=0.43)	0.40	0.02
Lipids, μm/mg/dL								
Total cholesterol	0.25±0.55 (*P*=0.66)	−1.12±1.34 (*P*=0.40)	−2.08±1.24 (*P*=0.10)	0.03±0.55 (*P*=0.96)	0.64±0.82 (*P*=0.43)	0.08±0.52 (*P*=0.88)	0.17	0.44
HDL cholesterol	0.37±1.76 (*P*=0.83)	2.52±4.33 (*P*=0.56)	0.24±4.07 (*P*=0.95)	−0.98±1.72 (*P*=0.57)	3.40±2.61 (*P*=0.20)	−0.58±1.64 (*P*=0.73)	0.78	0.11
LDL cholesterol	0.72±0.67 (*P*=0.28)	−0.38±1.62 (*P*=0.82)	−2.54±1.49 (*P*=0.09)	0.59±0.66 (*P*=0.37)	0.60±1.00 (*P*=0.55)	0.53±0.63 (*P*=0.40)	0.11	0.92
Triglycerides	−0.21±0.20 (*P*=0.28)	−0.67±0.47 (*P*=0.16)	−0.26±0.43 (*P*=0.54)	−0.20±0.19 (*P*=0.30)	−0.01±0.30 (*P*=0.97)	−0.17±0.18 (*P*=0.36)	0.50	0.54
BMI, μm/kg/m^2								
Women	−2.79±6.04 (*P*=0.65)	−21.62±13.44 (*P*=0.11)	−4.56±12.97 (*P*=0.73)	−1.57±5.85 (*P*=0.79)	−5.02±8.05 (*P*=0.54)	−3.67±5.32 (*P*=0.49)	0.04	0.77
Men	−14.80±8.71 (*P*=0.09)	−9.12±23.50 (*P*=0.70)	−8.89±20.50 (*P*=0.67)	−9.58±8.78 (*P*=0.28)	−22.71±13.71 (*P*=0.10)	−7.01±8.18 (*P*=0.40)	0.62	0.06

TABLE 3. Continued

Continuous Predictor	Common Segments	Bifurcation Segments	Internal Segments	Near Walls	Far Walls	All Sites	Differences Among Segments (*P*)	Differences Between Walls (*P*)
Controls only								
Age, μm/y	7.08±1.45 (*P*<0.0001)	10.89±4.06 (*P*=0.008)	6.86±2.82 (*P*=0.02)	7.18±1.81 (*P*<0.0001)	6.76±1.61 (*P*<0.0001)	6.22±1.40 (*P*<0.0001)	0.62	0.62
Blood pressure, μm/mm Hg								
Systolic	1.18±0.74 (*P*=0.11)	2.68±1.99 (*P*=0.18)	1.50±1.40 (*P*=0.29)	0.88±0.92 (*P*=0.34)	1.33±0.80 (*P*=0.10)	1.24±0.70 (*P*=0.08)	0.65	0.62
Diastolic	−0.53±1.37 (*P*=0.70)	−2.26±3.69 (*P*=0.54)	−2.89±2.70 (*P*=0.29)	−1.18±1.73 (*P*=0.91)	−0.17±1.47 (*P*=0.91)	−0.27±1.31 (*P*=0.84)	0.19	0.55
Smoking, μm/pack-years	0.96±0.60 (*P*=0.11)	3.83±1.41 (*P*=0.008)	1.46±1.11 (*P*=0.19)	1.07±0.74 (*P*=0.15)	1.28±0.63 (*P*=0.05)	1.24±0.58 (*P*=0.04)	0.20	0.96
Glucose, μm/mg/dL	0.98±0.40 (*P*=0.02)	1.76±1.07 (*P*=0.10)	2.04±0.86 (*P*=0.02)	0.89±0.50 (*P*=0.08)	0.91±0.44 (*P*=0.04)	0.78±0.39 (*P*=0.05)	0.17	0.99
Lipids, μm/mg/dL								
Total cholesterol	0.25±0.34 (*P*=0.47)	0.32±0.89 (*P*=0.72)	0.78±0.63 (*P*=0.22)	0.41±0.41 (*P*=0.31)	0.19±0.36 (*P*=0.60)	0.20±0.32 (*P*=0.54)	0.36	0.93
HDL-cholesterol	−0.99±0.83 (*P*=0.23)	−2.26±2.20 (*P*=0.31)	−0.57±1.52 (*P*=0.71)	−0.35±1.00 (*P*=0.73)	−1.29±0.89 (*P*=0.15)	−0.65±0.79 (*P*=0.41)	0.94	0.19
LDL-cholesterol	0.36±0.40 (*P*=0.36)	0.58±1.04 (*P*=0.58)	0.85±0.73 (*P*=0.24)	0.48±0.48 (*P*=0.31)	0.39±0.43 (*P*=0.36)	0.31±0.37 (*P*=0.41)	0.36	0.72
Triglycerides	0.05±0.09 (*P*=0.58)	0.04±0.23 (*P*=0.86)	0.12±0.15 (*P*=0.44)	0.00±0.11 (*P*=0.98)	0.08±0.09 (*P*=0.38)	0.06±0.08 (*P*=0.47)	0.79	0.41
BMI, μm/kg/m^2								
Women	0.23±2.65 (*P*=0.93)	−3.20±6.52 (*P*=0.62)	8.84±4.94 (*P*=0.08)	0.68±2.64 (*P*=0.80)	1.07±3.03 (*P*=0.72)	0.97±2.49 (*P*=0.70)	0.04	0.73
Men	8.14±4.19 (*P*=0.06)	3.49±12.60 (*P*=0.78)	1.56±9.70 (*P*=0.87)	6.80±6.06 (*P*=0.27)	12.10±4.34 (*P*=0.007)	11.57±3.79 (*P*=0.003)	0.52	0.53

Values are slope±SE.

ments, walls, and all sites combined are illustrated in this table, the focus of this communication is related to level of statistical significance for differences in these associations among segments and between walls.

For the group as a whole, statistically significant differences ($P<0.05$) in relationships among segments were noted for age (strongest effect at bifurcation), prior history of hypertension (strongest effect at internal), body mass index (BMI) in women (strongest negative effect at bifurcation), and CAD status (strongest effect at bifurcation and internal segments). Statistically significant differences in risk factor relationships between walls were noted for glucose, prior history of diabetes, pack-years of smoking, and CAD status (which in all cases were stronger at the far wall). Sex, personal report of postmenopausal status (no menstrual periods for >1 year), LDL cholesterol, systolic blood pressure, and history of myocardial infarction each had statistically significant relationships with IMT at individual segments and/or walls, and these relationships were fairly homogeneous (ie, interactions were not significant).

In analysis restricted to cases, associations between IMT and age and prior history of hypertension varied among segments, similar to the group as a whole, and blood glucose and pack-years of smoking appeared to affect far walls more than near walls. In addition, for the group as a whole, systolic blood pressure was associated with increased IMT of all sites, but no segment or wall was uniquely affected.

Among controls, although many risk factors (age, sex, blood glucose, prior history of diabetes, pack-years of smoking, BMI, menopausal status, prior history of hypertension) were related to IMT (eg, 1 segment, 1 wall, or all sites), these relationships did not vary significantly among segments or between walls.

Discussion

It appears rational that the associations of risk factors with extracranial carotid atherosclerosis should be homogeneous and that all segments and both walls should be equally affected. Furthermore, the repeatability of IMT measurements varies among segments and is greatest for far walls and common segments.[6] These considerations support use of B-mode protocols that focus exclusively on the far wall of the common carotid artery. Few investigators have explored the possibility that risk factor associations might differ among segments of the extracranial carotid arteries. Tell et al[14] reported that age, hypertension, and cigarette smoking affected all segments evaluated equally, while sex and diabetes appeared to affect the bifurcation and internal carotid more than the common

TABLE 4. Relationships Between IMT and Subgroups: All Participants

Subgroup	Common Segments	Bifurcation Segments	Internal Segments	Near Walls	Far Walls	All Sites	Differences Among Segments (*P*)	Differences Between Walls (*P*)
All participants								
Sex								
Female	933±20	1499±50	1126±45	1108±26	1283±35	1168±26	0.31	0.38
Male	987±20	1612±50	1203±43	1159±26	1303±35	1202±26		
	(*P*=0.11)	(*P*=0.10)	(*P*=0.02)	(*P*=0.07)	(*P*=0.59)	(*P*=0.18)		
Ethnicity								
Black	958±48	1427±120	1151±120	1129±53	1318±68	1204±49	0.36	0.78
Other	966±15	1567±38	1166±33	1134±23	1291±30	1183±23		
	(*P*=0.87)	(*P*=0.26)	(*P*=0.90)	(*P*=0.93)	(*P*=0.69)	(*P*=0.65)		
Hypertension								
No	927±20	1470±50	1061±43	1096±26	1245±35	1149±26	0.04	0.76
Yes	1002±20	1638±49	1270±43	1169±26	1339±35	1221±26		
	(*P*=0.006)	(*P*=0.01)	(*P*=0.0004)	(*P*=0.01)	(*P*=0.01)	(*P*=0.005)		
Current smoking								
No	973±28	1577±69	1127±60	1132±24	1289±32	1182±24	0.11	0.30
Yes	963±17	1548±42	1179±37	1137±33	1305±43	1194±32		
	(*P*=0.73)	(*P*=0.71)	(*P*=0.44)	(*P*=0.89)	(*P*=0.70)	(*P*=0.68)		
Diabetes								
No	950±16	1512±40	1125±35	1125±24	1255±31	1171±23	0.47	0.002
Yes	1018±29	1707±73	1310±65	1163±35	1425±45	1236±33		
	(*P*=0.04)	(*P*=0.02)	(*P*=0.01)	(*P*=0.26)	(*P*<0.0001)	(*P*=0.03)		
Prior MI								
No	946±16	1495±40	1124±36	1119±23	1262±31	1168±23	0.06	0.20
Yes	1035±30	1769±73	1310±64	1182±35	1406±45	1245±33		
	(*P*=0.004)	(*P*=0.001)	(*P*=0.01)	(*P*=0.06)	(*P*=0.001)	(*P*=0.01)		
CAD status								
Control	903±19	1321±46	989±42	1074±25	1201±33	1127±25	<0.0001	0.008
Case	1027±19	1789±46	1344±41	1192±25	1390±33	1246±25		
	(*P*<0.0001)	(*P*<0.0001)	(*P*<0.0001)	(*P*<0.0001)	(*P*<0.0001)	(*P*<0.0001)		
Cases only								
Sex								
Female	1018±32	1755±77	1286±72	1241±41	1477±57	1333±41	0.20	0.21
Male	1057±32	1862±76	1414±68	1301±40	1477±56	1384±40		
	(*P*=0.36)	(*P*=0.31)	(*P*=0.19)	(*P*=0.15)	(*P*=0.99)	(*P*=0.21)		
Ethnicity								
Black	1043±104	1518±248	1459±271	1312±108	1723±159	1496±103	0.59	0.05
Other	1038±24	1822±56	1347±52	1270±35	1467±47	1353±36		
	(*P*=0.96)	(*P*=0.23)	(*P*=0.69)	(*P*=0.69)	(*P*=0.11)	(*P*=0.16)		
Hypertension								
No	989±34	1700±82	1185±74	1220±42	1410±59	1309±42	0.02	0.80
Yes	1073±30	1888±70	1473±64	1310±38	1525±53	1395±39		
	(*P*=0.05)	(*P*=0.08)	(*P*=0.003)	(*P*=0.03)	(*P*=0.07)	(*P*=0.03)		
Current smoking								
No	1032±27	1825±64	1368±59	1266±37	1468±50	1353±37	0.45	0.21
Yes	1053±43	1765±102	1304±94	1287±49	1501±70	1373±49		
	(*P*=0.66)	(*P*=0.61)	(*P*=0.56)	(*P*=0.66)	(*P*=0.65)	(*P*=0.67)		
Diabetes								
No	1035±28	1794±65	1338±60	1273±37	1437±50	1353±38	0.92	0.008
Yes	1044±41	1844±97	1382±91	1268±48	1575±67	1373±47		
	(*P*=0.86)	(*P*=0.67)	(*P*=0.68)	(*P*=0.92)	(*P*=0.05)	(*P*=0.65)		
Prior MI								
No	1017±28	1765±67	1317±62	1255±38	1441±52	1339±38	0.76	0.82
Yes	1079±38	1891±91	1411±83	1303±45	1548±64	1394±45		
	(*P*=0.17)	(*P*=0.25)	(*P*=0.35)	(*P*=0.28)	(*P*=0.11)	(*P*=0.19)		

TABLE 4. Continued

Subgroup	Common Segments	Bifurcation Segments	Internal Segments	Near Walls	Far Walls	All Sites	Differences Among Segments (*P*)	Differences Between Walls (*P*)
Controls only								
Sex								
Female	876±19	1235±49	964±41	971±27	1092±33	989±22	0.14	0.84
Male	910±19	1370±50	981±41	1017±27	1125±33	1019±23		
	(*P*=0.20)	(*P*=0.05)	(*P*=0.72)	(*P*=0.15)	(*P*=0.25)	(*P*=0.22)		
Ethnicity								
Black	916±37	1378±100	996±84	1019±49	1123±47	1023±38	0.80	0.58
Other	890±14	1291±38	970±34	989±22	1106±30	1000±99		
	(*P*=0.51)	(*P*=0.41)	(*P*=0.76)	(*P*=0.55)	(*P*=0.68)	(*P*=0.55)		
Hypertension								
No	877±17	1282±47	955±39	981±26	1086±32	985±22	0.99	0.61
Yes	913±20	1326±53	996±43	1009±28	1135±34	1025±23		
	(*P*=0.17)	(*P*=0.53)	(*P*=0.42)	(*P*=0.39)	(*P*=0.08)	(*P*=0.17)		
Current smoking								
No	895±16	1272±41	981±35	997±23	1108±31	1014±20	0.07	0.63
Yes	882±27	1393±70	946±54	979±36	1109±39	999±29		
	(*P*=0.80)	(*P*=0.14)	(*P*=0.54)	(*P*=0.63)	(*P*=0.97)	(*P*=0.87)		
Diabetes								
No	881±14	1276±38	950±33	985±22	1093±30	993±19	0.26	0.53
Yes	863±33	1445±88	1126±68	1037±43	1192±44	1066±35		
	(*P*=0.02)	(*P*=0.08)	(*P*=0.01)	(*P*=0.24)	(*P*=0.01)	(*P*=0.04)		
Prior MI								
No	892±14	1291±38	975±33	994±22	1106±31	1001±19	0.29	0.99
Yes	900±43	1404±117	948±87	978±55	1128±53	1022±43		
	(*P*=0.87)	(*P*=0.36)	(*P*=0.76)	(*P*=0.77)	(*P*=0.65)	(*P*=0.62)		

Values are mean±SE. MI indicates myocardial infarction.

carotid. The report of Folsom et al[15] from the Atherosclerosis Risk in Communities Study appears to support this observation, although the results are reported in qualitative rather than quantitative terms. Tell et al[14] also noted that whites and blacks appeared to have similar distributions of IMT of the common carotid artery but that whites tended to have greater IMT in the bifurcation and internal carotid. The Cardiovascular Health Study reported segment-specific differences in relationships between IMT and race: common carotid IMT was thicker in black than white men and women, while internal carotid IMT was significantly thicker in white women.[16] In the Insulin Resistance Atherosclerosis Study (IRAS), blacks had greater mean common carotid IMT than non-Hispanic whites, and there was no significant difference in internal carotid IMT between blacks and non-Hispanic whites. Hispanics had lesser common carotid IMT than non-Hispanic whites and no differences in internal carotid IMT.[17] The IRAS has also shown greater common carotid IMT (but not internal carotid IMT) in established compared with newly diagnosed diabetics.[18] In a study comparing IMT in Mexico City residents with Mexican Americans living in San Antonio, Tex, age, male sex, high total cholesterol, low HDL, and high systolic blood pressure were associated with both common carotid and internal carotid IMT, whereas smoking was significantly associated only with internal carotid IMT. Common carotid and internal carotid IMT were both higher in diabetic than nondiabetic participants.[19] In the European Vascular Aging Study (EVA), diabetes and smoking were associated with IMT of the common carotid but not plaque (in the internal carotid and/or bifurcation), whereas increased cholesterol was related to plaque only.[20]

We have quantified associations of risk factors with individual segments and walls of the extracranial carotid arteries in 280 individuals with known coronary status. We found for the group as a whole that sex, postmenopausal status, LDL cholesterol, systolic blood pressure, and history of myocardial infarction all had statistically significant relationships with IMT at individual segments and/or walls, but no differences in these relationships among segments or between walls could be detected. On the other hand, and of considerable interest, we also found that certain risk factors had different associations with one or the other segment or wall of the carotid artery. In particular, age, prior history of hypertension, and BMI in women were associated with bifurcation/internal carotid disease more than with common carotid disease, and diabetes and smoking had stronger effects on the far wall than the near wall. CAD status had associations with IMT that varied both among segments and between walls. Unfortunately, the small number of blacks in our sample precluded us from identifying significant differences on the basis of race.

These observations have bearing on use of various protocols for identification of associations of risk factors

with extracranial carotid disease. We have used these data to estimate the relative efficiency of evaluating any particular site as opposed to all 12 sites for detecting cross-sectional relationships. Our analyses suggest that there may be no optimum subset of sites for the detection of cross-sectional relationships; none that we examined provided uniformly greater statistical power than the comparisons based on all walls for the full panel of risk factors addressed in our study. Thus, while investigators may wish to base cross-sectional relationships on analyses limited to a subset of sites, they cannot rule out the importance of measuring all 12 sites. Some evidence exists that the same may be the case for relationships with IMT progression. In the ACAPS, investigators found that if relationships were equal in magnitude across sites, the greatest statistical efficiency was obtained when progression rates were based on all 12 walls.[7] Of interest, we[8] and others[21,22] have previously made similar observations regarding the associations of extracranial carotid disease with prevalent and incident symptomatic vascular disease.

Certain limitations of these findings need to be mentioned. First, since these were cross-sectional measurements we cannot state that the associations we observed would pertain to progression of disease at one or another site. Second, since we excluded patients with prior history of endarterectomy, those with the most severe level of extracranial atherosclerosis have been excluded. Finally, by excluding patients with mildly obstructive coronary disease (<50% stenosis), we select those with the extremes of coronary status and lose some of the potential gradation of risk they might present.

We can only speculate broadly regarding the possible biological significance of these observations. Segments of the extracranial carotid arteries differ histologically, and segments and walls are differentially exposed to turbulent flow. The common carotid artery is a muscular artery, whereas the internal carotid artery is an elastic artery.[23] Conceivably these histological differences might increase or decrease the response of an arterial segment to one or another risk factor. Alternatively, turbulent flow is eccentric and complex in the extracranial carotid arteries and is most pronounced at the bifurcation and the internal carotid. The common carotid is less exposed to turbulent flow. Thus, a risk factor that affected the bifurcation or the internal carotid artery more than the common might be imagined to have a particular interaction with those forces that were associated with turbulent flow. Those factors that were particularly associated with disease that was eccentrically distributed might also be imagined to have an association with turbulent flow; however, the precise nature of this association is obscured by the complicated nature of atherosclerosis development in the setting of turbulent flow. Masawa et al[24] describe a helical pattern of atherosclerosis of the extracranial carotid arteries that affects most markedly the anterior (ventral) wall of the common carotid and bifurcation, the lateral and posterior wall of the transition between the bifurcation and the internal carotid, and the posterior (dorsal) wall of the mid internal carotid artery. Interrogation of the extracranial carotid arteries is often performed from several directions, and thus the precise anatomic position of the "near" or "far" wall depends on the angle of interrogation and may not be uniform for the common carotid, bifurcation, and internal carotid arteries of a given subject. Furthermore, in vitro comparisons of histology with near as opposed to far wall interrogation with B-mode show that ultrasonic identification of near wall IMT is less than that determined histologically because of a narrower intima in the ultrasonic IMT measurement.[25] For these reasons, the designation of "asymmetrical disease" is likely more precise than attribution of disease to near or far walls, per se.

In summary, our data demonstrate that many relationships between risk factors and IMT are heterogeneous among segments and between walls. This suggests protocols that include IMT measures from different segments and walls are prudent.

Acknowledgments

This study was supported by grants HL-35333 and HL-59503 from the National Heart, Lung, and Blood Institute and by the General Clinical Research Center of the Wake Forest University School of Medicine (MO1 RR-07122).

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