Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 1999;19:356-365
doi: 10.1161/01.ATV.19.2.356
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636

Relationships of Cerebral MRI Findings to Ultrasonographic Carotid Atherosclerosis in Older Adults

The Cardiovascular Health Study

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Abstract—Cerebral magnetic resonance imaging (MRI) has demonstrated a high prevalence of infarct-like lesions, white matter hyperintensities, and evidence of cerebral atrophy in older adults. While these findings are generally believed to be related to ischemia and atherosclerosis, their relationship to atherosclerosis in the carotid arteries remains to be explored. Study subjects were part of the multicenter Cardiovascular Health Study, a cross-sectional study of 3502 women and men ≥65 years of age undergoing cranial MRI and carotid ultrasonography. MRI infarcts were detected in 1068 participants (29.3%) and measurable carotid plaque in 2745 (75.3%). MRI infarcts, ventricular and sulcal widening, and white matter score were strongly associated with carotid intimal-medial thickness (IMT) and stenosis degree after adjustment for age and sex (all $P<0.01$). Associations with plaque characteristics were less strong and less consistent; MRI infarcts were weakly associated only with surface irregularity, and ventricular size was weakly associated only with lesion density (both $P<0.04$). In contrast, sulcal widening was strongly related to plaque characteristics, with scores being higher in those with heterogeneous and irregular plaque (both $P<0.009$). Adjustment for other risk factors, and for carotid IMT/stenosis, removed associations of MRI findings with plaque characteristics except for weak relationships remaining between MRI infarcts and surface irregularity and between sulcal score and heterogeneous plaque (both $P<0.03$). MRI abnormalities show strong and consistent relationships with increasing carotid IMT and stenosis degree but less strong associations with plaque characteristics, especially after adjusting for IMT and stenosis. **(*Arterioscler Thromb Vasc Biol*. 1999;19:356-365.)**

Key Words: stroke ■ cerebrovascular disorders ■ carotid arteries ■ atherosclerosis ■ aged ■ epidemiology ■ risk factors

Cerebral magnetic resonance imaging (MRI) has demonstrated a high prevalence of infarct-like lesions, white matter hyperintensities, and evidence of cerebral atrophy in older adults.[1–3] While these findings are related to standard risk factors for cardiovascular disease and are believed to be consequences of ischemia,[4–6] their relationship to atherosclerosis in the carotid arteries has not been widely explored.

Because the carotid arteries provide the majority of the brain's blood supply, detailed information on extent, severity, and characteristics of carotid atherosclerosis can be used to explore its relationships to cerebral MRI findings. Lesion characteristics such as increased density, heterogeneity, and surface irregularity have been shown to relate to prevalent clinically defined transient ischemic attack and stroke,[6] but these associations have not been examined for cerebral MRI findings.

The Cardiovascular Health Study (CHS) cohort represents a large, multicenter sample of older men and women examined by both carotid ultrasonography and cerebral MRI. Cross-sectional data from these examinations were analyzed (1) to describe prevalences of MRI-defined infarcts, infarct-like lesions, and gray and white matter changes by quintile of common and internal carotid intimal-medial thickness (IMT); degree of carotid stenosis; and characteristics of carotid plaque; (2) to determine independence of carotid atherosclerosis/MRI abnormality associations from known clinical and subclinical cardiovascular disease and cardiovascular disease risk factors; and (3) to define relationships of MRI infarcts and ipsilateral carotid artery disease.

Methods

CHS participants were recruited from a random sample of the Medicare eligibility lists of the Health Care Financing Administra-

Received February 20, 1998; revision accepted July 15, 1998.

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***Arterioscler Thromb Vasc Biol.* is available at http://www.atvbaha.org**

tion 4 US communities: Forsyth County, NC; Sacramento County, Calif; Washington County, Md; and Pittsburgh (Allegheny County), Pa. Details of design and methods have been previously published.[1,7,8] The baseline examinations were conducted between June 1989 and May 1990 for 5201 participants of the original cohort and between June 1992 and May 1993 for an additional 687 black participants. Carotid ultrasound was performed at entry for both cohorts and was repeated in the original cohort during the 1992 to 1993 examination. Cerebral MRI was performed in 1992 to 1994, spanning 2 annual examinations due to limited scanner availability, but is considered part of the 1992 to 1993 examination data set. Carotid data as well as other risk factors and clinical disease data used in the current analysis are limited to the 1992 to 1993 examination for all participants.

Carotid Ultrasound

Near- and far-wall maximal IMT of the carotid arteries were measured by trained readers and averaged as an indicator of atherosclerosis; separate measurements were made for common and internal carotid arteries. Plaque was defined as any focal thickening of the intimal-medial layer of the common or internal carotid arteries or carotid bulb. Stenosis degrees of <50% were judged visually as 1% to 24% or 25% to 49%. Stenosis of 50% to 74% was defined by duplex ultrasonography as Doppler peak flow velocity≥1.5 m/s; 75% to 99% as flow velocity≥2.5 m/s; and 100% stenosis as absent flow. Individual participants were characterized by the degree of stenosis in the most severely affected vessel; that is, a 100% left-sided stenosis and 25% right-sided stenosis would place a participant in the 100% stenosis category. CHS ultrasound methods and initial quality control results have been previously published.[9]

Focal lesions were evaluated on the basis of gray-scale images for texture, surface irregularity, and density. Lesion texture was classified as homogeneous or heterogeneous (uniform versus nonuniform echogenicity throughout lesion, respectively). Lesion surface was classified as smooth, mildly irregular (height variations≤0.4 mm), markedly irregular (height variations>0.4 mm), and ulcerated (discrete depression>2 mm in width extending into the media). Lesion density was characterized as calcified (hyperdense at one interface with acoustic shadowing underneath), hyperdense, isodense, or hypodense relative to uninvolved adjacent intima-media. Due to the small number of ulcerated lesions, the ulcerated and markedly irregular categories were combined for the purpose of analysis. Right- and left-sided analyses were limited to plaque characteristics of the most severe focal lesion, with severity defined hierarchically as above. Thus, a right carotid system with a homogeneous lesion at the bifurcation and a heterogeneous lesion in the internal carotid would be classified as having a heterogeneous plaque. Similarly, a participant with a smooth lesion in the right carotid system and a markedly irregular lesion in the left system would be classified as having markedly irregular plaque. Distributions and associations of plaque characteristics, as well as representative gray-scale images used to characterize them, have been previously published.[10]

Cerebral MRI

Cerebral MRI was performed according to a standard protocol.[1,11] Infarcts by MRI were defined as lesions with abnormal signal in a vascular distribution and no mass effect. Infarcts of the cortical gray matter and deep nuclear regions and capsule were defined as lesions bright on spin density and T_2-weighted images compared with normal gray matter and isointense or hypointense on T_1-weighted images. Infarcts in the cerebral white matter and brain stem were also bright on spin density and on T_2-weighted images but, in addition, were hypointense on T_1-weighted images, approximating the intensity of cerebrospinal fluid. In this report, presumed infarcts in any region were classified as "small infarct-like lesions" if <3 mm in size and as "MRI infarcts" when ≥3 mm in size. Intrareader and interreader reliability for MRI infarcts in the first 300 participants was high (κ=0.71 and 0.78, respectively) but not so for infarct-like lesions (κ=0.71 and 0.32 for intrareader and interreader, respectively). The protocol was thus modified to include duplicate readings of infarcts and small infarct-like lesions in all subjects. MRI infarcts and infarct-like lesions were classified without reference to clinical signs or symptoms; their relationship to symptoms and clinically recognized stroke has been reported previously.[12]

Cerebral ventricular size was assessed on a scale of 0 to 9 by comparison with a series of 8 studies with successively increasing ventricular size ranging from small (grade 1) to severe enlargement (grade 8). Studies considered to have ventricles smaller than those in grade 1 received grade 0, and worse than grade 8 received grade 9. Similarly, sulcal widening was assessed by comparison with 8 studies with successively increasing sulcal size, with grades 0 and 9 assigned for ventricular size. Focal atrophy was assessed as focal volume loss in brain parenchyma without abnormal signal intensity. Perivascular spaces were assessed in the high parietal convexity and inferior basal ganglia as lesions isointense on spin density images, bright on T_2 images, and dark on T_1 relative to gray matter. Bifrontal distance was the largest right-left diameter from the lateral border of the frontal horn of the right lateral ventricle to the corresponding point along the lateral border of the frontal horn of the left lateral ventricle. Inner table width was the largest right-left diameter from the inner table of the skull measured along the same line as the bifrontal diameter.

"White matter disease" was estimated as the total volume of periventricular and subcortical white matter signal abnormality on spin density–weighted axial images compared with 8 studies successively increasing from barely detectable white matter changes (grade 1) to extensive, confluent changes (grade 8). Studies with no white matter changes received grade 0, and those with changes worse than grade 8 received grade 9. White matter changes were also characterized for predominant location (periventricular versus subcortical). All studies were assessed without knowledge of information such as subject's age, gender, clinical disease status, prior imaging findings, or other cardiovascular disease risk factors. Intraclass correlation coefficients for repeated readings were 0.52 for sulcal scores, 0.74 for ventricular scores, 0.80 for white matter scores, 0.85 for bifrontal distance, and 0.80 for inner table distance. For analytic purposes, ventricular, sulcal, and white matter scores with very low frequencies were collapsed into the next most frequent category (0 combined with 1, and 6 and above combined into a single category). Design and methodology of the MRI study have been described previously.[1,11]

Statistical Analysis

Associations between MRI infarcts and infarct-like lesions with categorical and continuous variables were assessed by χ^2 testing and ANOVA, respectively. Associations between ultrasound and categorical MRI variables were assessed by logistic regression after adjustment for age and sex, though prevalence and associations differed little by sex. Significance levels were estimated for continuous measures of carotid IMT (despite use of quintiles for data presentation in tables), ordered categories for stenosis degree and surface irregularity, and unordered categories for lesion heterogeneity and density. Associations with continuous MRI variables were assessed by linear regression after adjustment for age and sex, with significance levels estimated as above. Associations between MRI characteristics and plaque characteristics were assessed only in persons with measurable plaque (n=2745). Multiple logistic or linear regression analyses assessing independent associations of ultrasound and categorical or continuous MRI variables, respectively, were estimated by allowing correlates of MRI variables identified in previous analyses to enter forward stepwise predictive models of each MRI variable separately.[3,7,13] Significant correlates were then forced into a model with each carotid variable separately. Because plaque characteristics have been shown to be strongly related to increasing IMT and carotid stenosis,[7] models for plaque characteristics were repeated with forced inclusion of IMT/stenosis in addition to other significant covariates. Prevalence of ipsilateral versus contralateral MRI infarcts were compared by χ^2 testing for the highest IMT quintile versus quintiles 1 to 4 and by presence or absence of stenosis≥50%, plaque irregularity, and hyperdense plaque in the right and left carotid arteries separately. Because of the large number of comparisons performed, associations at $P<0.01$ were considered to be statistically significant, and those at $0.01<P<0.05$ were considered to be of borderline significance. All analyses were performed using the SPSS/Windows System, version 6.1.

TABLE 1. Risk Factors and Clinical Characteristics of Participants With and Without MRI Infarcts and Infarct-Like Lesions

Characteristic	MRI Infarcts (With or Without Infarct-Like Lesions (n=1068)	Infarct-Like Lesions Only (n=185)	No MRI Infarcts or Infarct-Like Lesions (n=2238)	*P*
Age, y	76.0	75.3	74.6	0.0001
Male, %	43.7	43.8	40.5	0.2
Hypertension, %	58.6	49.2	47.1	0.001
Systolic BP, mm Hg	138.6	136.7	133.9	0.0001
Diastolic BP, mm Hg	72.1	72.3	70.4	0.0001
Total cholesterol, mg/dL	202.7	205.4	200.5	0.5
LDL-cholesterol, mg/dL	121.1	122.9	119.6	0.5
HDL-cholesterol, mg/dL	52.5	55.7	53.7	0.001
Current smoking, %	46.7	44.3	48.6	0.4
Past smoking, %	41.0	45.4	41.0	0.6
Diabetes, %	15.1	11.4	13.8	0.4
Creatinine, mg/dL	1.11	1.05	1.04	0.0001
Aspirin use >7 d/2 wk, %	37.2	32.1	29.3	0.001
Atrial fibrillation, %	3.5	3.3	2.6	0.4
Prior MI, %	12.8	8.1	7.6	0.001
Prior CABG, %	6.8	3.8	4.2	0.003
Prior CHF, %	6.9	2.2	3.7	0.001
Prior stroke, %	12.1	6.0	1.7	0.001
Prior TIA, %	5.8	2.7	1.7	0.001

Hypertension indicates blood pressure ≥160/95 or on medications; diabetes, fasting blood glucose ≥126 mg/dL or use of insulin or oral hypoglycemic medications; aspirin use, self-report of days of medication use in preceding two weeks; atrial fibrillation, present on ECG at entry or during routine follow-up exam; prior cardiovascular disease, self-report of physician diagnosis at any time prior to MRI; MI, myocardial infarction; CABG, coronary artery bypass grafting; CHF, congestive heart failure; and TIA, transient ischemic attack.

Results

Cerebral MRI was performed in 3660 participants, of whom 3502 also had carotid ultrasound data and MRI scans interpretable for presence of MRI infarcts. MRI infarcts were detected in 1068 of these 3502 participants while smaller infarct-like lesions (with or without MRI infarcts) were found in 467. Data on infarct-like lesions were missing in 11 participants. A total of 1253 participants had either MRI infarcts or small infarct-like lesions. Measurable plaque was detected in the right carotid in 2225 participants and in the left carotid in 2151 participants. MRI infarcts were associated with older age, higher blood pressures and creatinine levels, lower high-density lipoprotein cholesterol, more frequent aspirin use, and higher prevalences of prior cardiovascular disease (Table 1). Associations with infarct-like lesions were inconsistent but prevalence and levels, in general, were intermediate between those in participants with MRI infarcts and participants with neither MRI infarcts nor infarct-like lesions.

MRI infarcts were strongly associated with common and internal carotid IMT and degree of carotid stenosis after adjustment for age and sex (all $P<0.0001$, Figure 1). Participants in the highest quintile of common carotid IMT had 50% greater prevalence of MRI infarcts, and those in the highest quintile of internal carotid IMT had 40% greater prevalence, compared with those in the lowest quintile after adjustment for age and sex. Subjects with ≥75% stenosis were nearly twice as likely to have MRI infarcts as those without stenosis. In contrast, smaller infarct-like lesions were not associated with IMT or stenosis degree ($P>0.2$).

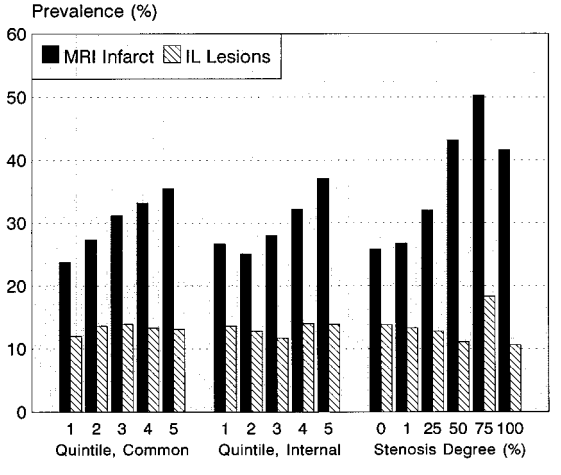

Figure 1. Prevalence of MRI infarcts and infarct-like (IL) lesions by atherosclerosis severity (quintiles defined by sex and 5-year age strata). Percentages adjusted for age and sex. All associations with MRI infarcts significant at $P<0.0001$; no associations with infarct-like lesions significant.

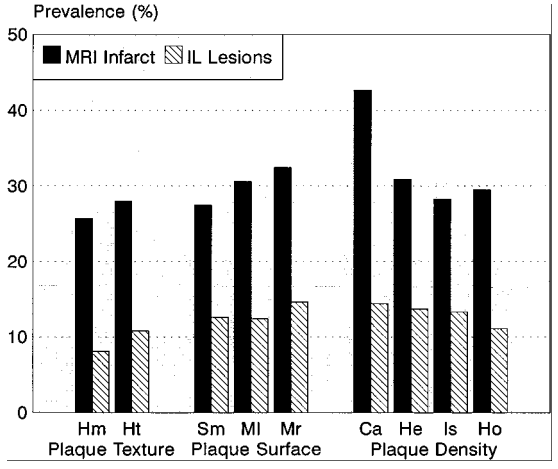

Figure 2. Prevalence of MRI infarcts and infarct-like (IL) lesions by atherosclerosis characteristics. Percentages adjusted for age and sex. Hm indicates homogenous; Ht, heterogeneous; Sm, smooth; MI, mildly irregular; Mr, markedly irregular/ulcerated; Ca, calcified; He, hyperdense; Is, isodense; and Ho, hypodense. Associations with MRI infarcts and lesion surface borderline significant at $P<0.04$; infarct-like lesions and lesion texture significant at $P<0.008$; no other associations significant.

Associations of MRI infarcts with plaque characteristics were less strong than for IMT and carotid stenosis (Figure 2) and reached significance only for surface irregularity; infarct prevalence increased modestly with increasing surface irregularity ($P<0.04$). Smaller infarct-like lesions were strongly associated with heterogeneous plaque ($P<0.008$), being 33% more common in those with heterogeneous versus homogeneous plaque.

Sulcal score was associated with all 6 carotid variables, including common and internal IMT and stenosis, heterogeneous texture, surface irregularity, and increased density (Table 2). The highest quintile of common carotid IMT was associated with a mean 0.13 U greater sulcal score compared with the lowest quintile. Ventricular size showed similar associations with IMT and stenosis but its only relation to plaque characteristics was a weak association with increased lesion density. Bifrontal distance was associated only with common carotid IMT, whereas focal atrophy showed no relationships at all with carotid variables (data not shown).

Severity of white matter disease increased with increasing IMT and stenosis but was not related to lesion characteristics after adjustment for age and sex, though there was a nonsignificant trend toward increased white matter disease with increasing surface irregularity and lesion density (Table 2, last column). The highest common carotid quintile had a mean 0.30 greater white matter score than the lowest quintile. Periventricular concentration of white matter disease and increased perivascular spaces were not related to carotid IMT, stenosis, or plaque characteristics (data not shown).

Multivariate analyses adjusting for factors in addition to age and sex showed common and internal carotid IMT to remain significantly associated with MRI infarcts after adjustment for age, sex, hypertension, echo-LVH, aspirin use (aspirin taken on more than 7 days in a 2 week period), systolic and diastolic blood pressures, creatinine, and smoking status (Table 3). A 0.25-mm increment in common carotid IMT (1 interquartile range difference) was associated with a 1.19-fold odds on presence of MRI infarct. Degree of carotid stenosis, particularly >50%, was also associated with increased prevalence of MRI infarcts. Plaque heterogeneity was not associated with MRI infarcts, but surface irregularity showed a weak inverse relationship ($P<0.03$) only when IMT and stenosis were included in the model. In contrast, lesion density showed a weak relationship ($P<0.02$) only when IMT and stenosis were not included in the model. This association was limited to calcified plaque, which had a nearly 2-fold increased prevalence of MRI infarct compared with isodense plaque. Infarct-like lesions were associated only with heterogeneous plaque texture, but this association was strong, independent of age, sex, diastolic blood pressure, and creatinine, and persisted after adjustment for IMT and stenosis.

Sulcal score was independently associated with IMT and stenosis as well as plaque heterogeneity, surface irregularity, and weakly to lesion density, after adjustment for age, sex, aspirin use, and hypertension (Table 4). A 0.25 mm increment in common carotid IMT was associated with a 0.07 unit increase in sulcal score after multiple adjustment. Further adjustment for IMT and stenosis weakened the relationship of sulcal score to heterogeneous plaque and removed it for surface irregularity and lesion density. Ventricular size was associated with IMT after adjustment for other covariates but was unassociated with plaque characteristics other than a trend toward increased size with plaque heterogeneity that disappeared after adjustment for IMT and stenosis.

Bifrontal distance was associated only with common carotid IMT (Table 5), after adjustment for inner table distance, age, sex, systolic blood pressure, atrial fibrillation, high-density lipoprotein cholesterol, and aspirin use, and showed no multivariate relationships with plaque characteristics. White matter disease was associated only with IMT after adjustment for age, sex, systolic and diastolic blood pressures, hypertension status, and smoking status. White matter disease was not associated with plaque characteristics though there were nonsignificant trends toward increased severity of white matter disease with surface irregularity and increased plaque density.

Examination of ipsilateral versus contralateral MRI infarcts related to disease in the right or left carotid artery showed little evidence of stronger associations on the ipsilateral side (Table 6), as might be suspected if carotid ultrasound were to detect vascular abnormalities leading to cerebral disease in the distribution of the ipsilateral carotid artery. Limiting analyses to MRI infarcts ≥15 mm in diameter or in watershed vascular distributions showed nearly identical associations with carotid atherosclerosis and plaque characteristics as shown for MRI infarcts as a group (data not shown).

Discussion

MRI infarcts, ventricular and sulcal widening, and white matter disease were strongly associated with carotid IMT and stenosis after adjustment for age, sex, and a variety of other cardiovascular and cerebrovascular disease risk factors in this population-based sample of older adults. Though MRI abnormalities showed some associations with plaque characteristics after adjustment for age and sex, many of these were eliminated after adjustment for other risk factors and for severity of carotid atherosclerosis. Only infarct-like lesions retained a significant association (with heterogeneous plaque) after multivariate adjustment; relationships of MRI infarcts

TABLE 2. Prevalence of Ventricular and Sulcal Widening by Carotid Atherosclerosis, Adjusted by Age and Sex

Ultrasound Characteristic	*n*	Sulcal Score, Mean	Ventricular Size, Mean	Adjusted* Bifrontal Distance, Mean	White Matter Score, Mean
Quintile of CC wall thickness, mm	3502				
≤0.893	700	3.33	3.54	3.55	2.13
0.894–0.995	756	3.41	3.56	3.58	2.18
0.996–1.085	665	3.40	3.53	3.56	2.18
1.086–1.212	730	3.39	3.66	3.58	2.34
≥1.213	651	3.46	3.65	3.61	2.43
P		0.002	0.01	0.005	0.0001
Quintile of IC wall thickness, mm	3501				
≤0.951	706	3.42	3.56	3.56	2.13
0.952–1.145	694	3.29	3.46	3.56	2.15
1.146–1.427	704	3.37	3.58	3.59	2.23
1.428–1.862	696	3.38	3.63	3.58	2.34
≥1.863	701	3.52	3.67	3.57	2.39
P		0.0004	0.009	0.21	0.0002
Degree of carotid stenosis, %	3496				
0	749	3.50	3.64	3.60	2.18
1–24	1152	3.39	3.64	3.62	2.26
25–49	1417	3.50	3.71	3.60	2.37
50–74	124	3.49	3.74	3.65	2.39
75–99	36	4.11	3.94	3.64	2.53
100	18	4.28	4.06	3.78	1.97
P		0.02	0.02	0.20	0.003
Plaque characteristics†	2732				
Homogeneous	1168	3.31	3.57	3.59	2.28
Heterogeneous	1564	3.49	3.66	3.59	2.31
P		<0.001	0.06	0.81	0.54
Lesion surface†	2745				
Smooth	1194	3.38	3.63	3.60	2.27
Mildly irregular	1192	3.47	3.69	3.61	2.37
Markedly irregular/ulcerated	359	3.58	3.70	3.60	2.39
P		0.002	0.17	0.5	0.07
Lesion density†	2734				
Calcified	76	3.61	3.78	3.56	2.57
Hyperdense	421	3.53	3.81	3.63	2.46
Isodense	1387	3.47	3.65	3.61	2.32
Hypodense	850	3.35	3.61	3.60	2.29
P		0.02	0.04	0.24	0.09

*Adjusted for inner table distance; †includes only subjects with measurable plaque.

(with decreasing surface irregularity) and sulcal widening (with heterogeneous plaque) were only of borderline significance after adjustment. There was no evidence of stronger associations of MRI infarcts with ipsilateral versus contralateral carotid disease, nor of differing associations for large (≥15 mm) or watershed infarcts.

Carotid Disease and the Brain

While carotid IMT and stenosis have been demonstrated to have strong associations with clinically-evident stroke,[10,14,15] CT-defined infarcts,[16,17] and more recently with MRI-defined infarcts,[18,19] less information is available on relationships of atherosclerosis severity to other MRI abnormalities such as

TABLE 3. Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for MRI Infarcts and Infarct-Like Lesions by Carotid Characteristics

	MRI Infarcts*		Infarct-Like Lesions†	
Ultrasound Characteristic	No Adjustment for IMT/Stenosis OR [95% CI]	Adjustment for IMT/Stenosis OR [95% CI]	No Adjustment for IMT/Stenosis OR [95% CI]	Adjustment for IMT/Stenosis OR [95% CI]
Common carotid wall thickness, 0.25 mm increment	1.19 [1.08,1.31]	...	1.05 [0.93,1.17]	...
P	0.0004		0.43	
Internal carotid wall thickness, 0.735 mm increment	1.26 [1.12,1.40]	...	1.08 [0.95,1.23]	...
P	0.0001		0.25	
Degree of carotid stenosis, %				
1–24	0.99 [0.78,1.25]	...	0.94 [0.71,1.24]	...
25–49	1.22 [0.97,1.54]	...	0.94 [0.72,1.23]	...
50–74	1.81 [1.16,2.84]	...	0.74 [0.40,1.38]	...
75–100	2.43 [1.32,4.48]	...	1.32 [0.62,2.81]	...
P	0.002		0.78	
Plaque texture				
Heterogeneous	1.06 [0.88,1.28]	0.87 [0.71,1.08]	1.39 [1.10,1.76]	1.41 [1.09,1.83]
P	0.51	0.21	0.006	0.009
Lesion surface				
Mildly irregular	1.05 [0.86,1.27]	0.86 [0.69,1.06]	0.97 [0.76,1.24]	0.94 [0.72,1.23]
Markedly irregular/ulcerated	1.09 [0.82,1.44]	0.68 [0.48,0.96]	1.23 [0.88,1.73]	1.08 [0.70,1.64]
P	0.52	0.03	0.45	0.93
Lesion density				
Calcified	1.98 [1.19,3.28]	1.73 [1.03,2.90]	1.32 [0.69,2.51]	1.27 [0.66,2.44]
Hyperdense	1.07 [0.82,1.38]	0.96 [0.73,1.25]	1.10 [0.80,1.50]	1.06 [0.77,1.47]
Hypodense	1.02 [0.83,1.26]	1.10 [0.89,1.36]	0.81 [0.62,1.06]	0.82 [0.62,1.07]
P	0.02	0.15	0.22	0.33

*Models for MRI infarcts adjusted for gender, age at MRI, hypertension status (normal, borderline, and hypertensive), abnormal LV mass indicator (≥194 for women, ≥267 for men), aspirin use >7 days/2 weeks, systolic and diastolic blood pressure, creatinine, and smoking status (never, former, current).

†Models for small infarct-like lesions adjusted for gender, age at MRI, diastolic blood pressure, and creatinine.

ventricular and sulcal widening and white matter disease. Previous analyses from the CHS have demonstrated strong and graded relationships between white matter disease and carotid IMT and stenosis[3] and between ventricular and sulcal enlargement and severity of carotid atherosclerosis.[2] Given the strong and consistent relationships of MRI abnormalities to severity of carotid atherosclerosis, the question arises whether there are other ultrasound-definable characteristics of carotid disease that are related to MRI abnormalities.

Clinical studies of carotid atherectomy specimens suggest that ulcerated,[20] less organized,[15] and hemorrhagic[21,22] plaques are associated with symptoms. Some of these associations have been disputed, however, with other investigators failing to demonstrate more frequent symptoms associated with ulcerations[14,21] and plaque hemorrhage.[23,24] The documented ability of B-mode ultrasonographic scanning to detect plaque ulceration,[25] heterogeneity,[26,27] and hemorrhage,[28] though disputed by some,[24,29,30] has led to the demonstration that these ultrasound-defined characteristics are also associated with ipsilateral neurologic symptoms,[31] clinical events,[26] and MRI-defined infarcts.[18,32]

The mechanisms by which carotid artery disease may be associated with neurological symptoms and stroke include (1) thrombotic occlusion of large vessels such as the carotid and middle cerebral arteries with hypoperfusion in the vascular distribution supplied by these vessels; (2) cerebral embolism of either atheromatous material from a ruptured or ulcerated carotid plaque or of fibrin-platelet material from a thrombotic plaque to distal vessels; or (3) manifestation or general marker of systemic atherosclerosis occurring at the large and small vessel level. Previous studies have demonstrated a strong relationship between CT-defined small cerebral infarcts and ulcerated carotid plaque, even suggesting that small CT lesions may be markers of active plaque ulceration.[33] Pathological evidence of embolic material in small arteries supplying infarcted tissue[34] and clinical trials demonstrating reduced stroke incidence after carotid endarterectomy in persons with severe carotid stenosis[35] provide support for a direct pathogenic role of carotid disease in clinically evident stroke, but the smaller and more frequently silent infarcts detected by MRI may not share the same pathogenic mechanisms.

MRI Infarcts and Plaque Characteristics

The strong relationship of MRI infarcts to severity of carotid atherosclerosis as measured by IMT and stenosis does not

TABLE 4. Estimated Increment and 95% Confidence Intervals (CI) for Sulcal and Ventricular Scores by Carotid Characteristics

	Sulcal Score*		Ventricular Score†	
Ultrasound Characteristic	No Adjustment for IMT/Stenosis Increment [95% CI]	Adjustment for IMT/Stenosis Increment [95% CI]	No Adjustment for IMT/Stenosis Increment [95% CI]	Adjustment for IMT/Stenosis Increment [95% CI]
Common carotid wall thickness, 0.25 mm	0.07 [0.02,0.11]	...	0.05 [0.01,0.09]	...
P	0.003		0.02	
Internal carotid wall thickness, 0.735 mm	0.10 [0.04,0.15]	...	0.07 [0.02,0.11]	...
Degree of carotid stenosis, %				
1–24	−0.09 [−0.19,0.01]	...	0.01 [−0.09,0.10]	...
25–49	0.02 [−0.08,0.11]		0.06 [−0.03,0.16]	
50–74	0.01 [−0.21,0.22]		0.07 [−0.13,0.28]	
75–100	0.65 [0.24,0.96]		0.30 [0.00,0.60]	
P	<0.0001		0.21	
Plaque characteristics				
Heterogeneous	0.19 [0.10,0.27]	0.11 [0.01,0.21]	0.08 [0.00,0.16]	0.04 [−0.06,0.14]
P	<0.0001	0.03	0.06	0.44
Lesion surface				
Mildly irregular	0.08 [−0.01,0.17]	0.01 [−0.09,0.11]	0.06 [−0.03,0.14]	0.02 [−0.08,0.13]
Markedly irregular/ulcerated	0.21 [0.07,0.35]	0.03 [−0.14,0.20]	0.09 [−0.04,0.22]	−0.01 [−0.18,0.17]
P	0.009	0.95	0.27	0.86
Lesion density				
Calcified	0.12 [−0.14,0.38]	0.07 [−0.20,0.33]	0.11 [−0.14,0.36]	0.10 [−0.18,0.38]
Hyperdense	0.07 [−0.06,0.19]	0.01 [−0.12,0.13]	0.11 [0.00,0.23]	0.12 [−0.01,0.26]
Hypodense	−0.10 [−0.20,−0.01]	−0.07 [−0.17,0.03]	−0.03 [−0.12,0.06]	−0.02 [−0.13,0.08]
P	0.03	0.47	0.11	0.22

*Models for sulcal score adjusted for gender, age at MRI, hypertension, and aspirin use.
†Models for ventricular score adjusted for gender, age at MRI, hypertension status (normal, borderline, hypertensive), and aspirin use.

help to distinguish among the above possibilities, but associations of MRI infarcts with surface irregularity and heterogeneous (presumably hemorrhagic[29]) plaque would support artery-to-artery embolism of atherothrombotic material. That these associations were relatively weak and inconsistent, particularly after adjusting for IMT/stenosis, does not lend support for a direct pathogenic mechanism. Limiting analyses to large or watershed infarcts, which are more likely to be due to large-vessel atherosclerosis than to small-vessel hypertensive disease,[2,36] did not increase the strength of relationships with carotid plaque characteristics and thus also fails to support a direct pathogenic role for carotid disease. Conversely, the strong and consistent associations of small infarct-like lesions with plaque heterogeneity, especially given the lack of association of these lesions with carotid atherosclerosis severity and many other cardiovascular disease risk factors, raises questions about the pathogenesis of these mysterious lesions that may merit further investigation.

Similarly, the lack of association of MRI infarcts with plaque characteristics in the ipsilateral carotid artery does not support these lesions being manifestations of carotid arterial disease. That associations with carotid atherosclerosis severity did not differ between ipsilateral and contralateral arteries is puzzling, given prior pathologic and clinical trial evidence. These findings are consistent with data from over 800 patients in the Asymptomatic Carotid Atherosclerosis Study,[37] though they conflict with smaller studies showing associations with ipsilateral disease.[16,17] One explanation is that MRI detects far more small lesions than large ones,[2] which, as described above, are less likely to be related to atherosclerotic large-vessel disease.[36]

MRI-Defined Gray and White Matter Changes

Little is known about the significance or pathogenesis of increased ventricular and sulcal sizes and increased bifrontal distance, but they are generally believed to indicate loss of functioning cerebral tissue[38] and to be related to cognitive decline.[39] Given their generally symmetric nature, one might not expect to find them in association with unilateral carotid stenosis or high-risk plaque, but if ultrasound-defined carotid disease is a general marker of systemic atherosclerosis, as appears to be the case,[10] then some relationships with these MRI abnormalities might be expected. Carotid IMT was related to all these findings even after adjustment for other cardiovascular disease risk factors, but plaque characteristics for the most part were not, suggesting that these atrophic changes are more strongly related to atherosclerosis severity than to any particular type of carotid plaque.

TABLE 5. Estimated Increment and 95% Confidence Intervals (CI) for Bifrontal Distance and White Matter Disease Score by Carotid Characteristics

	Bifrontal Distance*		White Matter Score†	
Ultrasound Characteristic	No Adjustment for IMT/Stenosis Increment [95% CI]	Adjustment for IMT/Stenosis Increment [95% CI]	No Adjustment for IMT/Stenosis Increment [95% CI]	Adjustment for IMT/Stenosis Increment [95% CI]
Common carotid wall thickness, 0.25 mm	0.02 [0.01,0.04]	...	0.05 [0.00,0.10]	...
P	0.001		0.03	
Internal carotid wall thickness, 0.735 mm	0.02 [0.00,0.03]	...	0.07 [0.02,0.13]	...
P	0.06		0.01	
Degree of carotid stenosis, %				
1–24	0.03 [0.00,0.06]	...	0.00 [−0.11,0.12]	...
25–49	0.02 [−0.02,0.05]		0.11 [0.00,0.22]	
50–74	0.06 [−0.01,0.13]		0.07 [−0.17,0.31]	
75–100	0.10 [0.00,0.20]		0.02 [−0.32,0.37]	
P	0.12		0.19	
Plaque characteristics				
Heterogeneous	0.00 [−0.03,0.02]	−0.01 [−0.04,0.02]	0.01 [−0.09,0.11]	−0.04 [−0.16,0.08]
P	0.77	0.41	0.87	0.54
Lesion surface				
Mildly irregular	0.02 [−0.01,0.05]	0.02 [−0.02,0.05]	0.09 [−0.01,0.19]	0.09 [−0.04,0.21]
Markedly irregular/ulcerated	0.01 [−0.03,0.06]	0.00 [−0.05,0.05]	0.14 [−0.01,0.30]	0.09 [−0.12,0.29]
P	0.43	0.53	0.09	0.38
Lesion density				
Calcified	−0.06 [−0.14,0.03]	−0.07 [−0.15,0.02]	0.28 [−0.01,0.57]	0.27 [−0.06,0.59]
Hyperdense	0.02 [−0.02,0.06]	0.02 [−0.02,0.06]	0.12 [−0.02,0.26]	0.13 [−0.02,0.29]
Hypodense	−0.01 [−0.04,0.02]	−0.00 [−0.04,0.03]	−0.02 [−0.13,0.09]	−0.01 [−0.13,0.11]
P	0.28	0.31	0.07	0.15

*Models for bifrontal distance adjusted for inner table distance, gender, age at MRI, systolic blood pressure, history of atrial fibrillation, HDL-cholesterol, and aspirin use.

†Models for white matter disease adjusted for gender, age at MRI, systolic and diastolic blood pressure, hypertension status, and smoking status.

Less is known about the significance or pathogenesis of white matter disease, though it appears to be related to cognitive decline and dementia[40] and is associated most strongly with age and hypertension[3] as well as with atherosclerosis.[6] The current study confirmed its association with atherosclerosis severity but showed no significant associations with particular plaque characteristics, though there was a suggestion of relationships with surface irregularities and hypodense plaque that may deserve further investigation. Given the generalized nature of white matter disease, its association with carotid atherosclerosis severity but not plaque characteristics may reflect a relationship with more generalized vascular disease rather than implicating an etiologic role for a specific form of carotid disease.

Limitations of the current study include the relatively selected nature of the subgroup undergoing MRI, though with the high prevalence of carotid disease and MRI infarct in this subgroup, selection bias is unlikely to have a major impact on evaluating associations.[41] Reproducibility of plaque characteristics was relatively modest, with κ values in the 0.4 to 0.5 range, consistent with moderate reproducibility.[42] Improved methods of plaque characterization may enhance the identification of associations with MRI abnormalities, but future investigations should consider the strong correlation between tissue characteristics of plaque and atherosclerosis severity measured by wall thickness and stenosis. Because including severity measures in models of tissue characteristics may constitute overadjustment (in which severity may be an intermediate in any potential etiologic pathway between tissue characteristics and MRI abnormalities) presentation of analyses with and without adjustment for severity is probably prudent.

In summary, cerebral MRI findings were strongly related to carotid atherosclerosis severity but bore little relationship to ultrasound-defined plaque characteristics after adjustment for carotid IMT and stenosis. While the role of carotid atherosclerosis in cerebrovascular disease as detected by MRI remains to be defined, these data do not support an increased risk of cerebral MRI abnormalities in association with specific carotid plaque characteristics.

TABLE 6. Prevalence of Ipsilateral and Contralateral MRI Infarcts by Atherosclerosis Severity and Plaque Characteristics

	Right Carotid		Left Carotid	
	Ipsilateral, %	Contralateral, %	Ipsilateral, %	Contralateral, %
CC wall thickness, mm				
≥1.213	23.2	22.4	24.4	23.1
≤1.212	18.5	18.4	17.8	18.6
P	0.005	0.01	<0.0001	0.008
IC wall thickness, mm				
≥1.863	24.0	24.3	23.5	23.1
≤1.862	18.2	17.9	18.1	18.6
P	0.0005	0.0001	0.001	0.009
Carotid stenosis, %				
≥50	31.4	29.4	30.9	29.1
<50	19.0	19.0	18.8	19.1
P	0.002	0.009	0.001	0.009
Plaque texture				
Heterogeneous	22.5	23.1	20.7	20.8
Homogeneous	19.9	20.3	19.7	21.5
P	0.13	0.11	0.55	0.68
Plaque surface				
Markedly irregular/ulcerated	26.2	24.6	23.2	24.0
Mildly irregular/smooth	20.8	21.4	19.9	20.8
P	0.08	0.31	0.24	0.25
Plaque density				
Hyperdense/calcified	23.2	25.1	24.6	24.2
Hypodense/isodense	20.5	20.4	18.1	19.6
P	0.17	0.02	0.0004	0.02

Acknowledgments

This work was supported by contracts N01-HC-5079, N01-HC-85086, and N01-HC-15093 from the National Heart, Lung, and Blood Institute.

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