Carotid Artery Atherosclerosis, MRI Indices of Brain Ischemia, Aging, and Cognitive Impairment
The Framingham Study

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Background and Purpose—Carotid atherosclerosis has been associated with increased risk of stroke and poorer cognitive performance in older adults. The relation of carotid atherosclerosis to cognitive impairment and MRI indices of ischemia and aging in midlife is less clear.

Methods—We studied 1975 Framingham Offspring Study participants free of stroke and dementia with available carotid ultrasound, brain MRI, and neuropsychological testing. We related common and internal carotid artery intima-media thickness and internal carotid stenosis to large white matter hyperintensity (>1 SD above age-specific mean), total brain volume, hippocampal volume, silent cerebral infarcts, and neuropsychological measures of verbal memory, executive function, and nonverbal memory measures.

Results—We observed that internal carotid artery intima-media thickness, but not common carotid artery intima-media thickness, was associated with higher prevalence of silent cerebral infarcts (OR, 1.21; 95% CI, 1.03–1.43; $P<0.05$), large white matter hyperintensity (OR, 1.19; 95% CI, 1.03–1.38; $P<0.05$), lower total brain volume (−0.05 per SD; $P<0.05$), and poorer performance in verbal memory (−0.06 per SD; $P<0.05$) and nonverbal memory measures (−0.08 per SD; $P<0.01$), but not with hippocampal volume. Internal carotid stenosis ≥25% was associated with a higher prevalence of large white matter hyperintensity (adjusted OR, 1.77; 95% CI, 1.25–2.53) and lower total brain volume (−0.11 per SD; $P=0.042$) but not with silent cerebral infarcts or hippocampal volume. Internal carotid stenosis ≥50% was associated with higher prevalence of silent cerebral infarcts (OR, 2.53; 95% CI, 1.17–5.44), large white matter hyperintensity (OR, 2.35; 95% CI, 1.08–5.13), and poorer performance on executive function (−0.39 per SD; $P<0.05$), but not with total brain volume or hippocampal volume.

Conclusions—Carotid atherosclerosis markers were associated with MRI indices of brain ischemia and aging and with cognitive impairment in a community-based sample of middle-aged adults. Our data suggest that internal carotid artery intima-media thickness may be a better marker for cognitive impairment than common carotid artery intima-media thickness. (***Stroke***. 2009;40:1590-1596.)

Key Words: atherosclerosis ■ brain MRI ■ carotid ■ cognitive performance

Atherosclerosis of the carotid artery is an important mechanism underlying cerebrovascular disease, and it has been associated with stroke, cognitive impairment,[1,2] and dementia.[3] Whereas the majority of studies evaluating the relation of carotid atherosclerosis and cognitive function have been performed in symptomatic patients[4,5] with severe stenosis, recent population-based studies also have suggested that asymptomatic carotid atherosclerosis is related to poorer neuropsychological (NP) performance,[1,2,6] even with mild degrees of stenosis.[1] Traditional vascular risk factors have been associated with both carotid atherosclerosis[7] and cognitive impairment,[8,9] but the pathophysiology of these processes remains unclear and understanding of their relation is limited.

Carotid stenosis and carotid intima-media thickness (IMT) reflect different stages and severity of the atherosclerotic process. Although IMT is considered a marker of subclinical atherosclerosis, the relations between hypertension, atherosclerosis, and measures of carotid IMT are complex and likely reflect the interaction of both processes, whereas carotid stenosis more accurately reflects the atherosclerotic process. Both carotid stenosis and IMT are related to cardiovascular events within and outside the brain, such as stroke and myocardial infarction.[10]

IMT studies, however, have also found strong associations with MRI findings and NP measures, particularly among older individuals.[2,11]

Site-specific differences in carotid measures of atherosclerosis may be important in their role in cerebrovascular disease, brain injury, and cognitive impairment. Previous studies have shown differences in severity of these measures, depending on the site of evaluation.[12] In addition, other studies suggest that carotid site-specific differences may relate differentially to vascular risk factors,[13,14] and progression rates of carotid measures differ depending on the arterial site studied.[15,16]

The atherosclerotic process as measured by carotid IMT or mild stenosis may relate to decreased cognitive performance via structural changes measurable at MRI, such as large white matter hyperintensities (LWMH), silent cerebral infarcts (SCI),[17,18] and decreased total brain volume, decreased cognitive performance via atherosclerotic vascular disease even in the absence of demonstrable structural change, the independent impact of vascular risk factors such as increasing levels of systolic blood pressure on cognition, or through all 3 mechanisms.

We hypothesize that carotid atherosclerosis, as reflected by IMT and stenosis, relates to MRI markers of brain ischemia and aging, and also to poorer cognitive performance. This relation may vary depending on the site of IMT measurement (ie, common carotid artery [CCA] vs internal carotid artery [ICA]) and the measure used (stenosis or IMT).

Subjects and Methods

Study Sample
The Framingham Offspring Cohort was recruited in 1971 and has been examined periodically every ≈4 to 8 years.[19] Carotid duplex ultrasound was conducted during the sixth examination cycle (1995–1998), and brain MRI and cognition were assessed during the seventh examination cycle (1999–2001). Of the 3380 participants who underwent carotid ultrasound, 2028 also underwent brain MRI and NP testing; 57 were excluded because of prevalent clinical stroke, dementia, multiple sclerosis, or other neurological conditions that could affect MRI measures, yielding a study sample of n=1971. The Institutional Review Board of Boston University Medical Center approved the study protocol and informed consent was obtained from all subjects.

Carotid Ultrasound
Carotid ultrasound was acquired by a certified sonographer, following a standard protocol.[20] Ultrasound studies were conducted on 3377 of 3532 (96%) of examination cycle 6 participants. An ultrasound device equipped with a high-resolution linear-array transducer with color Doppler and Doppler spectral analyzer (Model SSH-140A; Toshiba America Medical Systems) was used. Common carotid arteries were imaged with a 7.5-MHz transducer, whereas a 5-MHz transducer (−3 dB point 6.2 MHz) was used to image the carotid bulb and the internal carotid arteries. Images were gated to an ECG and taken at end diastole (peak of the R-wave).

Determination of Carotid Stenosis
One image was taken of the distal CCA, 2 were taken of the carotid artery bulb, and 2 were taken of the proximal 2 cm of the ICA. The images were analyzed by 1 operator and over-read by an experienced radiologist (J.F.P.). Hemodynamically significant stenosis (≥50%) was defined by peak-systolic velocities ≥150 cm/sec. If peak systolic velocities were <150 cm/sec, the degree of stenosis was divided in 3 groups by an experienced sonographer: 0 (no stenosis), 1% to 24%, and 25% to 49%. The side with more severe degree of ICA stenosis

was used. The Framingham Heart Study intrareader reproducibility of carotid stenosis ≥25% has been previously reported (Kappa value=0.69).[21]

Measurements of IMT
IMT was measured bilaterally at 3 sites of the carotid arteries: CCA, carotid bulb, and ICA. The mean of the maximal IMT measurements of the near and far walls (maximum 4 artery walls were used for the CCA). The internal carotid/bulb IMT was defined as the mean of the 4 maximal IMT measurements made in the carotid artery bulb and the ICA on both sides, for a maximum of 16 wall segments. Good intraclass correlation coefficients for the mean and maximum ICA IMT and CCA IMT have been reported (0.74, 0.74, 0.86, and 0.90, respectively, based on 25 readings by 2 separate readers).[22]

Brain MRI Measurements
MRI scans were processed and analyzed by a neuroradiologist (C.D.) who was blinded to the subjects' demographic and clinical information, and to the carotid ultrasound measures. The acquisition and data processing of MRI scans has been described previously in detail.[23,24] In brief, the analyses were performed using semiautomated measurements of pixel distributions based on mathematical modeling of MRI pixel intensity histograms. This was performed for cerebral spinal fluid and brain (white matter and gray matter) to determine the optimal pixel intensity threshold to best distinguish cerebral spinal fluid from brain matter. All analyses were performed using a custom-designed image analysis package (QUANTA 6.2, operating on a Sun Microsystems Ultra 5 workstation).

Determination of brain volume was performed manually in coronal sections by outlining the intracranial cavity above the tentorium to determine the total cranial volume. Next, the skull and other nonbrain tissues were removed from the image, and mathematical modeling was performed to measure total brain volume. Of note, total brain volume excludes cerebrospinal fluid and includes the supratentorial gray and white matter. The ratio of total brain volume to total cranial volume (TCBV) was used as a measure of brain volume to correct for head size differences.

Hippocampal volume was determined manually in coronal sections. The hippocampus was defined to include fields CA1 to CA4, in addition to the dentate gyrus and the subicular complex. The coronal 3-dimensional MR data set was first resliced for alignment perpendicular to the long axis of the hippocampal formation on the left side, followed by manual outline of the hippocampus borders in the anterior to posterior direction, on 1.5-mm-thickness coronal slices, verifying the boundaries in the corresponding sagittal and axial views. Hippocampal volume was also analyzed as percent of total cranial volume.

The method used to determine abnormal white matter hyperintensities volume also has been published previously. The inter-rater reliabilities range between 0.90 and 0.94 for total cranial volume, TCBV, and white matter hyperintensities, and intrarater reliabilities average 0.98 across all measures.[25,26] The intrarater reliability for both right and left hippocampus using the method described are 0.98 for the right and 0.96 for the left hippocampus. LWMH was defined as log white matter hyperintensity areas >1 SD above the age-specific mean.[25,26] The presence or absence of SCI was determined manually by the operator based on the size (≥3 mm), location, and imaging characteristics of the lesion (cerebrospinal fluid signal intensity on subtraction images; proton density T2 and hyperintense on T2-weighted images), and using previously described methods.[26]

NP Tests
Trained examiners administered a comprehensive NP test battery during a single 50-minute session using standard protocols. To reduce the number of individual test comparisons, individual tests were grouped in factors, using factor analysis.[27] This approach identified factors related to specific cognitive domains, including verbal memory factor (Wechsler Memory Scale Logical Memory, Paragraph A subtest, Immediate and Delayed Recall), executive function factor (Halstead Reitan Trail Making Tests A and B), and

nonverbal memory factor (Boston Naming Test, Wechsler Adult Intelligence Scale Similarities subtest, and Hooper Visual Orientation Test). We selected these 3 factors as outcome measures to evaluate the relation with carotid atherosclerosis measures because previous studies suggest that in subjects with high vascular risk factor burden, the pattern of cognitive impairment predominantly involves attention and psychomotor speed, whereas verbal memory is affected mostly in subjects with amnestic cognitive impairment (such as seen in Alzheimer disease). The nonverbal memory factor provides assessment of additional cognitive functions including language, abstract reasoning, and visuoperceptual skills.

Covariates

Stroke risk factors, measured at the sixth examination cycle, were defined as follows: systolic blood pressure, recorded as the average of 2 physician measurements; use of an antihypertensive drug; current cigarette smoking; diabetes mellitus, defined as a random blood glucose of ≥126 mg/dL, a previous diagnosis of diabetes or using hypoglycemic medication or insulin; history of atrial fibrillation; and previous cardiovascular disease, including coronary heart disease, heart failure, and peripheral arterial disease.[28]

Statistical Analysis

Multivariable regression analyses were used to determine the associations of carotid atherosclerosis measures with brain MRI markers and with NP factors. Separate analyses were performed to investigate each of the 4 measures of carotid atherosclerosis. Two cutpoints of carotid stenosis were evaluated. The cutpoint of 25% for carotid stenosis has been related to several vascular risk factors in previous carotid ultrasound studies in Framingham and other cohorts,[29] and the 50% threshold represents hemodynamically significant stenosis used in clinical practice. ICA IMT and CCA IMT were each log-transformed to normalize their skewed distributions and were standardized using z-scores, so that the regression analyses provide estimates of the effect of change in IMT of 1 SD.

Logistic regression analyses were performed for dichotomous outcomes (SCI, LWMH) and results are given as OR with 95% CI. Linear regression analyses were used for continuous outcomes (TCBV, hippocampal volume, NP factors), and results are given as standardized beta coefficients (and their standard errors) reflecting, in SD units, the effect of each measure of carotid atherosclerosis. All analyses were adjusted for age and sex, stroke risk factors and the time interval between carotid ultrasound and acquisition of brain MRI and NP testing. To address possible confounding by the MRI markers, we performed additional analyses of NP outcomes adjusted for LWMH, TCBV, and SCI. The effect of side of carotid atherosclerosis measures on NP performance was also evaluated (left vs right). All analyses were determined a priori and performed using Statistical Analyses System software version 9.1 (SAS Institute). A 2-sided $P<0.05$ was considered statistically significant.

Results

Baseline demographic data for the study participants at the sixth examination cycle are shown in Table 1. There were no significant differences in clinical characteristics of subjects included and excluded from the present analysis. Hippocampal volume measurements were available in a subset of 787 participants (mean age, 64 years; 52% women) who were significantly older than those without hippocampal volume measurements, but they did not differ in any of the other stroke risk factors. Carotid artery stenosis ≥25% was observed in 289 participants (14.7%) and carotid stenosis ≥50% was observed in 35 participants (1.8%). In brain MRI we observed LWMH in 306 participants (15.5%), and SCI was observed in 206 participants (11%). Mean TCBV (SD) was 0.78 (0.03), and the mean hippocampal volume (SD) was 0.31 (0.04). Performance in NP

Table 1. Characteristics of Study Sample, Sex-Specific Subsamples, and Excluded Subjects

	Included Men and Women (n=1971)	Excluded Men and Women (n=1561)
Clinical characteristics		
Women	53%	53%
Age at sixth examination, yr, mean±SD	58±10	61±10
Age at MRI, yr, mean±SD	62±9	
Systolic blood pressure, mm Hg, mean±SD	126±18	131±19
Diabetes mellitus	8.7%	12.3%
Atrial fibrillation	2.2%	4.5%
Electrocardiographic left ventricular hypertrophy	0.3%	1.2%
Current smokers	13.6%	17.4%
Hypertension treatment	24.1%	33.8%
Prevalent cardiovascular disease	7.5%	13.9%
Carotid ultrasound measures		
Carotid stenosis ≥25%	14.7%	
Carotid stenosis ≥50%	1.8%	
MRI measures		
SCIs, %	11%	
LWMH volume, %	15.5%	
TCBV, mean±SD	0.78±0.03	
Hippocampal volume, N=787, mean±SD	0.31±0.04	

testing according to carotid atherosclerosis measures is shown in Table 2.

Relation of Carotid Atherosclerosis Measures and Brain MRI Markers

Carotid stenosis ≥25% and ≥50% were both related to SCI and LWMH and inversely related to TCBV. Participants with ≥25% stenosis had a higher prevalence of SCI (OR, 1.64; 95% CI, 1.14–2.36; $P=0.007$), a higher prevalence of LWMH (OR, 1.76; 95% CI, 1.27–2.45; $P<0.001$), and lower brain volume ($\beta=-0.21\pm$standard error [SE] 0.05; $P<0.001$). After adjusting for vascular risk factors and the time between acquisition of carotid ultrasound and MRI and NP testing, the associations remained significant with LWMH (OR, 1.77; 95% CI, 1.25–2.53; $P=0.001$) and brain volume ($\beta=-0.11\pm$SE 0.06; $P=0.04$), but not with SCI.

Carotid stenosis ≥50% was also associated with an increased prevalence of SCI (OR, 3.07; 95% CI, 1.46–6.42; $P=0.003$) and of LWMH (OR, 2.26; 95% CI, 1.06–4.80; $P=0.03$), and with lower brain volume ($\beta=-0.28\pm$SE 0.14; $P=0.047$). After the full multivariable adjustment, carotid stenosis ≥50% was associated with SCI (OR, 2.53; 95% CI, 1.17–5.44; $P=0.02$), and with LWMH (OR, 2.35; 95% CI, 1.08–5.13; $P=0.03$).

We observed that ICA IMT was significantly associated with a higher prevalence of SCI (OR, 1.33; 95% CI, 1.14–1.55; $P<0.001$) and LWMH (OR, 1.23; 95% CI, 1.07–1.42;

Table 2. Relation of Carotid Atherosclerosis Measures, MRI Measures, and NP Factors Performance

	Carotid Stenosis*			Log (IMT)*		Carotid Stenosis†		Log (IMT)†
	≥25%	≥50%	CCA	ICA	≥25%	≥50%	CCA	ICA
MRI measures (95% CI)								
SCI (95% CI)	1.64	3.07	1.20	1.33	1.35	2.53	1.09	61.21
	(1.14–2.36)‡	(1.46–6.42)‡	(1.03–1.41)§	(1.14–1.55)¶	(0.92–1.98)	(1.17–5.44)§	(0.93–1.29)	(1.03–1.43)§
LWMH (95% CI)	1.76	2.26	1.10	1.23	1.77	2.35	1.09	1.19
	(1.27–2.45)¶	(1.06–4.80)§	(0.95–1.26)	(1.07–1.42)‡	(1.25–2.53)¶	(1.08–5.13)§	(0.94–1.27)	(1.03–1.38)§
TCBV (SE)	−0.21±0.05¶	−0.28±0.14§	−0.06±0.02‡	−0.10±0.02¶	−0.11±0.06§	−0.18±0.14	−0.02±0.02	−0.05±0.02§
Hippocampal volume (SE)	−0.01±0.10	0.01±0.23	−0.05±0.04	−0.01±0.04	0.09±0.1	0.11±0.28	−0.02±0.04	0.03±0.04
NP factors								
Verbal memory	−0.08±0.07	0.03±0.17	0.02±0.03	−0.03±0.03	−0.12±0.07	−0.02±0.18	0.01±0.03	−0.06±0.03§
Executive function	−0.16±0.07§	−0.42±0.17§	−0.01±0.03	−0.08±0.03‡	−0.09±0.07	−0.39±0.18§	0.02±0.03	−0.05±0.03
Nonverbal memory	−0.14±0.07§	−0.15±0.17	−0.02±0.03	−0.09±0.03¶	−0.12±0.07	−0.13±0.18	−0.01±0.03	−0.08±0.03‡

*Adjusted for age and sex.

†Additionally adjusted for time to MRI/NP, diabetes, smoking, hypertension treatment, systolic blood pressure, and cardiovascular disease. *P* shown when significant.

‡*P*<0.01.

§*P*<0.05.

¶*P*<0.001.

LWMH >1 SD age-specific. TCBV shows cranial-to-brain volume ratio. Effects on SCI and LWMH are OR and 95% CI. TCBV, hippocampal volume, and NP factors show standardized beta correlation coefficients and SE.

P=0.003), and with lower brain volume ($\beta=-0.10\pm$SE 0.02; *P*<0.001). All of the associations remained significant when using the full multivariable-adjusted model, with the increase in odds of having LWMH for each 1 SD increase in age in log-transformed baseline ICA IMT value (OR, 1.19; 95% CI, 1.03–1.38), and with brain volume decreasing by 0.05 per 1 SD increase in log-transformed baseline ICA IMT value (SE, 0.02; *P*=0.02). CCA IMT was also associated with higher prevalence of SCI (OR, 1.20; 95% CI, 1.03–1.41; *P*=0.02) and with lower brain volume ($\beta=-0.06\pm$SE 0.02; *P*=0.003), but these associations were no longer significant in the full multivariable-adjusted model.

Neither carotid stenosis nor IMT were associated with hippocampal volume, possibly because of the smaller sample size (N=787) with available hippocampal volume measurements.

Relation of Carotid Atherosclerosis Measures and NP Factors

Carotid stenosis ≥25% was associated with poorer performance on the executive function factor ($\beta=-0.08\pm$SE 0.03; *P*=0.002) and nonverbal memory factor ($\beta=-09\pm$SE 0.03;

P=0.001), but not with the verbal memory factor. After full multivariable adjustment, there was a trend for association with poorer performance on verbal memory and nonverbal memory factors, but the associations did not reach statistical significance (Table 3). Carotid stenosis ≥50% was associated with poorer performance only on the executive function factor ($\beta=-0.42\pm$SE 0.18; *P*=0.02). After the full multivariable adjustment, the association remained significant with persons with carotid stenosis ≥50% scoring a mean of 0.39 SD lower as compared to those with stenosis <50% (*P*<0.03). There was no significant association of carotid stenosis ≥50% with performance on verbal memory and nonverbal memory factors.

Higher ICA IMT was associated with poorer performance on the executive function factor ($\beta=-0.08\pm$SE 0.03; *P*=0.002) and the nonverbal memory factor ($\beta=-0.09\pm$SE 0.03; *P*=0.001). After full multivariable adjustment, the association became significant for the verbal memory factor ($\beta=-0.06\pm$SE 0.03; *P*=0.047) remained significant for the nonverbal memory factor ($\beta=-0.08\pm$SE 0.03; *P*=0.005), and was borderline for the executive function factor ($\beta=-0.05\pm$SE

Table 3. Carotid Atherosclerosis Measures and NP Factors Performance Adjusted for MRI Measures

	Carotid Stenosis*		Log (IMT)*		Carotid Stenosis†		Log (IMT)†	
	≥25%	≥50%	CCA	ICA	≥25%	≥50%	CCA	ICA
Verbal memory	−0.09±0.07	0.01±0.17	0.01±0.03	−0.04±0.03	−0.12±0.07	−0.03±0.18	0.01±0.03	−0.06±0.03§
Executive function	−0.11±0.07	−0.35±0.17§	0.001±0.03	−0.06±0.03§	−0.06±0.07	−0.34±0.17§	0.02±0.03	−0.04±0.03
Nonverbal memory	−0.12±0.07	−0.13±0.17	−0.02±0.03	−0.08±0.03‡	−0.10±0.07	−0.12±0.18	−0.01±0.03	−0.08±0.03‡

*Adjusted for age and sex.

†Additionally adjusted for time to MRI/NP testing, diabetes, smoking, hypertension treatment, systolic blood pressure, and cardiovascular disease.

‡*P*<0.01.

§*P*<0.05.

Effects on NP factors are standardized beta correlation coefficient (SE). *P* shown when significant.

0.03; P=0.053). CCA IMT was not associated with any of the cognitive measures.

Additional adjustment for the MRI markers (SCI, LWMH, TCBV, and hippocampal volume), which have been associated with cognitive impairment, did not alter the results (data not shown). We did not observe an effect of side (left vs right) in the association of carotid atherosclerosis measures and cognitive performance.

Discussion

Carotid atherosclerosis considered clinically asymptomatic was significantly related to poorer cognitive performance and to subclinical brain MRI indices of ischemia. These associations were significant even after adjusting for contemporaneously measured vascular risk factors, suggesting that carotid atherosclerosis measures provide additional information over vascular risk factors in relation to cognitive performance. MRI markers did not explain the association, suggesting that the association of carotid atherosclerosis with cognitive function was not confounded by structural brain changes. Carotid stenosis and IMT may represent past exposure to vascular risk factors, and therefore may provide valuable information over vascular risk factors.

Relation of Carotid Atherosclerosis and MRI Markers

Although it may be argued that carotid atherosclerosis measures and MRI indices of brain injury reflect the effects of exposure to vascular risk factors and systemic atherosclerosis, the results of our study suggest that carotid ultrasound measures of atherosclerosis are independent markers of brain MRI changes.

Our data add to findings of previous studies such as the Cardiovascular Health Study (mean age, 75 years) by using highly reliable techniques to quantitatively measure brain and white matter hyperintensity volumes. We expand previous results to a younger cohort (mean age, 58 years) including men and women with lower prevalence of vascular risk factors, in addition to using milder degrees of carotid stenosis. Investigators of the Cardiovascular Health Study evaluated the relation of carotid stenosis and IMT to MRI markers including SCI, WMH, and sulcal and ventricular enlargement.[30] Using subjective grading scales of brain MRI, the authors found that carotid IMT and stenosis related to the MRI markers after adjusting for vascular risk factors. The findings in our study are in agreement, suggesting that carotid atherosclerosis is likely a marker of morphometric brain changes assessed by MRI.

SCI were more common in association with more severe degrees of atherosclerosis, as reflected by a stronger association with stenosis ≥50% than with stenosis ≥25%. This is similar to findings in the Cardiovascular Health Study, in which subjects with stenosis had more MRI infarcts than did those without.[30] Although the associations of CCA and ICA IMT with SCI were significant after adjusting for age and sex, only the association with ICA IMT remained significant after adjustment for vascular risk factors. This finding contrasts with the observations in the Cardiovascular Health Study and suggests that vascular risk factors play a more important role in the relation of CCA IMT and SCI, because our cohort had

lower prevalence of vascular risk factors than those in the Cardiovascular Health Study.

The association of carotid atherosclerosis with decreased brain volume as measured in our study is a novel observation. Although it had been indirectly suggested by measures of sulcal widening and ventricular enlargement in the Cardiovascular Health Study,[30] we used volumetric quantitative measurement of brain volume, which was not reported previously in association with carotid atherosclerosis. We observed a 5% decrease in total brain volume per 1 SD increase in log-transformed ICA IMT after full multivariable adjustment. Given that few participants had hemodynamically significant stenosis ≥50%, it is unlikely that significant hemodynamic reduction in cerebral flow was responsible; carotid atherosclerosis may be a marker of brain atrophy related to involvement of microcirculation, systemic atherosclerosis, or other factors such as inflammation.[31]

IMT has been considered a subclinical marker of early atherosclerosis, although the relation with hypertension is complex, and increased IMT likely reflects effects of both processes. The observed association of increased ICA IMT with SCI, LWMH, and decreased total brain volume suggests that the process of atherosclerosis is not "silent" in subclinical stages, and the brain is affected during those phases. Whether aggressive evaluation and treatment of carotid atherosclerosis are useful to prevent the development of brain MRI changes or cognitive impairment is a question that cannot be answered with this study and deserves further attention. This is particularly relevant because of available therapies that may affect the atherosclerotic process in subclinical stages such as statins, which have been shown to reduce progression of IMT.[32,33] Our data suggest that IMT measured at the ICA may be a better marker of brain MRI changes than CCA IMT.

Relation of Carotid Atherosclerosis Measures and Cognitive Performance

Carotid atherosclerosis was related to lower cognitive performance. Our data are supportive of findings in previous studies such as the Cardiovascular Health Study,[2] which found high-grade (>75%) left-side, but not right-side, ICA stenosis and IMT related to poorer cognitive performance after adjusting for right-side stenosis, vascular risk factors, and demographic characteristics. Increased CCA IMT (fourth vs first quartiles) also was associated with lower cognitive performance, but no difference was found between the left and right sides. Similar to the results in the Cardiovascular Health Study cohort, we found that carotid stenosis and IMT were associated with poorer cognitive performance. More severe stenosis (≥50%) was associated with poorer performance, whereas milder stenosis (≥25%) did not reach statistical significance. We did not observe a different relation between left-side and right-side measures and cognitive performance, even though there was an effect of side in the relation of carotid stenosis and LWMH.

In addition, data from our study suggest that site of IMT measurement is important and that ICA IMT may be a better marker of poorer cognitive performance than CCA IMT. In contrast to previous studies, including the Cardiovascular Health Study,[2] ARIC,[9] Tromsø,[1] and Rotterdam[3] studies, we

separately evaluated the relation of IMT measured in the CCA and ICA to cognitive performance. Increased ICA IMT was associated with poorer performance but CCA IMT was not, after adjusting for vascular risk factors. Previous studies have shown that site of measurement of IMT may be relevant because associations with cardiovascular events and vascular risk factors may vary depending on the site of measurement.[10] Atherosclerosis develops earlier in vessel bifurcations and origins such as the carotid bulb and proximal ICA. As opposed to the Cardiovascular Health Study results, the association of increased IMT with poorer cognitive performance in our study persisted after adjustment for vascular risk factors. As noted, the Framingham Offspring cohort had a lower prevalence of vascular risk factors; thus, it may be possible that vascular risk factors explain the relation of CCA IMT, but not ICA IMT, with cognitive performance.

Because it may be argued that the association of carotid atherosclerosis with poorer cognitive performance is mediated by brain structural changes such as those assessed with brain MRI, we also evaluated the effect of MRI markers on the association of carotid atherosclerosis and cognitive performance. The associations remained significant after adjusting for the MRI measures, which supports that carotid atherosclerosis is an independent marker of poor cognitive performance.

We confirm the findings of previous studies by expanding the results by using a larger sample and quantitative assessment of MRI markers. The Cardiovascular Health Study[2] found an association of high-grade left ICA stenosis and poorer cognitive performance in a subset of subjects without brain infarct demonstrated by MRI, but did not evaluate the presence of white matter hyperintensities or brain volume. The Tromsø Study[1] was limited by small sample of subjects with brain MRI.

The precise underlying mechanism explaining the relation of carotid atherosclerosis and cognitive performance in our study is unclear, but as in the case of MRI markers, it is unlikely that hemodynamic effects explain the findings, because most of the participants had lower grades of stenosis. Our results suggest that carotid IMT and stenosis may have different effects on cognitive performance.

Strengths and Limitations

The present study has several strengths, including a large sample size, inclusion of both men and women, a middle-aged population, the community-based sample, use of reproducible quantitative carotid ultrasound techniques, quantitative brain MRI techniques, and interpretation of ultrasound and brain MRI imaging data by separate experienced readers, independent of one another and blinded to all clinical data. Our data expand the results of previous studies and support previous observations.

One of the limitations of our study is the assessment of carotid, MRI, and NP measures at single time points. As a result, we cannot draw conclusions regarding the cause–effect relationship between carotid atherosclerosis measures, brain MRI markers, and cognitive performance. In addition, carotid measures were assessed an average of 4 years before brain MRI and NP measures; hence, they may have changed in the interim. We attempted to address the noncontempora-

neous assessment by adjusting for the interval, and the results were largely unchanged. Another limitation is the fact that Framingham Heart Study participants are of predominantly white European descent; thus, generalization of our findings to other ethnic and racial groups is limited and requires additional study. We acknowledge that we did not account for multiple statistical testing, but we derive some reassurance from the consistency of the findings across correlated phenotypes and with the previous literature. Obviously, the results of this study should not be taken as justification for surgical intervention in patients with asymptomatic carotid stenosis.

Conclusion

Carotid atherosclerosis markers are associated with subclinical indices of brain ischemia and aging assessed via volumetric brain MRI, and with poorer cognitive performance after adjusting for standard vascular risk factors in a community-based sample of middle-aged adults free of clinical stroke and dementia. Further analysis of our data suggests that carotid atherosclerosis may have effects on cognition independent of MRI changes. Our findings are consistent with regional variation in the relation of carotid atherosclerosis measures, brain MRI markers of ischemia, and cognitive performance, and they support the notion that carotid atherosclerosis in subclinical stages is not truly silent.

Disclosures

Romero, Seshadri, Vasan, Polak, Beiser and Wolf had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design was performed by Romero, Seshadri, Beiser, Polak, and Wolf. Acquisition of data performed by Seshadri, Vasan, Au, Beiser, and Polak. Analysis and interpretation of data performed by Romero, Seshadri, Beiser, Polak, and Wolf. Drafting of the manuscript performed Romero, Seshadri, and Beiser. Critical revision of the manuscript for important intellectual content performed by Romero, Seshadri, Beiser, Benjamin, and Wolf. Statistical analysis performed by Beiser. Funding obtained by Vasan, Benjamin, Polak, and Wolf. Administrative, technical, or material support performed by Seshadri and Wolf. Study supervision performed by Seshadri and Wolf.

References

1. Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bonaa KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis: The Tromso study. *Neurology*. 2004;62:695–701.
2. Johnston SC, O'Meara ES, Manolio TA, Lefkowitz D, O'Leary DH, Goldstein S, Carlson MC, Fried LP, Longstreth WT Jr. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. *Ann Intern Med*. 2004;140:237–247.
3. van Oijen M, de Jong FJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Atherosclerosis and risk for dementia. *Ann Neurol*. 2007;61: 403–410.
4. Bo M, Massaia M, Speme S, Cappa G, Strumia K, Cerrato P, Ponzio F, Molaschi M. Cognitive function after carotid endarterectomy: Greater risk of decline in symptomatic patients with left internal carotid artery disease. *J Stroke Cerebrovasc Dis*. 2005;14:221–228.

5. Mocco J, Wilson DA, Komotar RJ, Zurica J, Mack WJ, Halazun HJ, Hatami R, Sciacca RR, Connolly ES Jr, Heyer EJ Predictors of neuro-cognitive decline after carotid endarterectomy. *Neurosurgery.* 2006;58: 844–850.

6. Komulainen P, Kivipelto M, Lakka TA, Hassinen M, Helkala EL, Patja K, Nissinen A, Rauramaa R. Carotid intima-media thickness and cog-nitive function in elderly women: a population-based study. *Neuroepide-miology.* 2007;28:207–213.

7. Fine-Edelstein JS, Wolf PA, O'Leary DH, Poehlman H, Belanger AJ, Kase CS, D'Agostino RB. Precursors of extracranial carotid atheroscle-rosis in the framingham study. *Neurology.* 1994;44:1046–1050.

8. Cerhan JR, Folsom AR, Mortimer JA, Shahar E, Knopman DS, McGovern PG, Hays MA, Crum LD, Heiss G. Correlates of cognitive function in middle-aged adults. Atherosclerosis risk in communities (ARIC) study investigators. *Gerontology.* 1998;44:95–105.

9. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology.* 2001;56:42–48.

10. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. *N Engl J Med.* 1999;340:14–22.

11. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam study. *BMJ.* 1994;308:1604–1608.

12. Heiss G, Sharrett AR, Barnes R, Chambless LE, Szklo M, Alzola C. Carotid atherosclerosis measured by b-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. *Am J Epidemiol.* 1991;134:250–256.

13. Yanez ND III, Kronmal RA, Shemanski LR, Psaty BM. A regression model for longitudinal change in the presence of measurement error. *Ann Epidemiol.* 2002;12:34–38.

14. Rubba P, Panico S, Bond MG, Covetti G, Celentano E, Iannuzzi A, Galasso R, Belisario MA, Pastinese A, Sacchetti L, Mancini M, Salvatore F. Site-specific atherosclerotic plaques in the carotid arteries of middle-aged women from southern Italy: Associations with traditional risk factors and oxidation markers. *Stroke.* 2001;32:1953–1959.

15. Mackinnon AD, Jerrard-Dunne P, Sitzer M, Buehler A, von Kegler S, Markus HS. Rates and determinants of site-specific progression of carotid artery intima-media thickness: The carotid atherosclerosis progression study. *Stroke.* 2004;35:2150–2154.

16. Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O'Leary DH, Haffner SM. Diabetes and progression of carotid atherosclerosis: The insulin resistance atherosclerosis study. *Arterioscler Thromb Vasc Biol.* 2003;23:1035–1041.

17. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med.* 2003;348:1215–1222.

18. O'Brien JT, Ames D. White matter lesions in depression and Alzheimer's disease. *Br J Psychiatry.* 1996;169:671.

19. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol.* 1979;110:281–290.

20. Polak JF, O'Leary DH, Kronmal RA, Wolfson SK, Bond MG, Tracy RP, Gardin JM, Kittner SJ, Price TR, Savage PJ. Sonographic evaluation of carotid artery atherosclerosis in the elderly: Relationship of disease severity to stroke and transient ischemic attack. *Radiology.* 1993;188: 363–370.

21. Elosua R, Ordovas JM, Cupples LA, Fox CS, Polak JF, Wolf PA, D'Agostino RA Sr, O'Donnell CJ. Association of apoE genotype with carotid atherosclerosis in men and women: The Framingham heart study. *J Lipid Res.* 2004;45:1868–1875.

22. Elosua R, Cupples LA, Fox CS, Polak JF, D'Agostino RA Sr, Wolf PA, O'Donnell CJ, Ordovas JM. Association between well-characterized lipoprotein-related genetic variants and carotid intimal medial thickness and stenosis: The Framingham heart study. *Atherosclerosis.* 2006;189: 222–228.

23. DeCarli C, Maisog J, Murphy DG, Teichberg D, Rapoport SI, Horwitz B. Method for quantification of brain, ventricular, and subarachnoid csf volumes from MR images. *J Comput Assist Tomogr.* 1992;16:274–284.

24. Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, D'Agostino RB, DeCarli C. Stroke risk profile, brain volume, and cognitive function: The Framingham offspring study. *Neurology.* 2004;63:1591–1599.

25. Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C. Stroke risk profile predicts white matter hyperintensity volume: The Framingham study. *Stroke.* 2004;35:1857–1861.

26. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, Beiser A, D'Agostino R, Wolf PA. Measures of brain morphology and infarction in the Framingham heart study: Establishing what is normal. *Neurobiol Aging.* 2005;26:491–510.

27. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of Alzheimer disease: A 22-year prospective study of the Framingham cohort. *Arch Neurol.* 2000;57:808–813.

28. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: A risk profile from the Framingham study. *Stroke.* 1991;22:312–318.

29. Wilson PW, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, O'Leary D, Wolf PA. Cumulative effects of high choles-terol levels, high blood pressure, and cigarette smoking on carotid steno-sis. *N Engl J Med.* 1997;337:516–522.

30. Manolio TA, Burke GL, O'Leary DH, Evans G, Beauchamp N, Knepper L, Ward B. Relationships of cerebral MRI findings to ultrasonographic carotid atherosclerosis in older adults: The cardiovascular health study. CHS collaborative research group. *Arterioscler Thromb Vasc Biol.* 1999; 19:356–365.

31. Jefferson AL, Massaro JM, Wolf PA, Seshadri S, Au R, Vasan RS, Larson MG, Meigs JB, Keaney JF Jr, Lipinska I, Kathiresan S, Benjamin EJ, DeCarli C. Inflammatory biomarkers are associated with total brain volume: The Framingham heart study. *Neurology.* 2007;68:1032–1038.

32. Yu CM, Zhang Q, Lam L, Lin H, Kong SL, Chan W, Fung JW, Cheng KK, Chan IH, Lee SW, Sanderson JE, Lam CW. Comparison of intensive and low-dose atorvastatin therapy in the reduction of carotid intimal-medial thickness in patients with coronary heart disease. *Heart.* 2007;93: 933–939.

33. Ozaki K, Kubo T, Imaki R, Shinagawa H, Fukaya H, Ohtaki K, Ozaki S, Izumi T, Aizawa Y. The anti-atherosclerotic effects of lipid lowering with atorvastatin in patients with hypercholesterolemia. *J Atheroscler Thromb.* 2006;13:216–219.