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Carotid Intima-Media Thickness and Cerebrovascular Disease in Community-Dwelling Older People Without Stroke

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Background and Purpose—Carotid intima-media thickness (CIMT) is a noninvasive measure of atherosclerosis, but it is unclear whether it is a stronger risk factor for large vessel disease or small vessel disease.

Methods—One hundred seven volunteers, aged 75 to 81 years, underwent measurements of CIMT and vascular risk factors and brain MRI (structural and diffusion tensor); those with history of stroke were excluded.

Results—In 96 subjects without stroke, there were significant associations between CIMT and markers of large vessel disease (carotid stenosis: $\rho=0.28$; $P=0.01$) and intermediary risk factors (systolic blood pressure: $\rho=0.34$; $P=0.001$). However, there were no significant associations between CIMT and markers of small vessel disease (white matter lesion load and water diffusion parameters).

Conclusions—CIMT was not associated with neuroimaging biomarkers of small vessel disease in older volunteers without stroke. Any association between CIMT and white matter lesion in previous studies is likely to be mediated via common intermediary risk factors like hypertension. **(*Stroke*. 2010;41:2083-2086.)**

Key Words: carotid intima media thickness ■ cerebrovascular disease ■ diffusion tensor ■ magnetic resonance imaging ■ white matter lesions

Carotid intima-media thickness (CIMT) is a noninvasive measure of atherosclerosis burden and is associated with future stroke risk.[1] It is unclear, however, whether CIMT is a stronger risk factor for large vessel disease (LVD) or small vessel disease (SVD).[2,3] Some of this apparent discrepancy may be because of incorrect classification of cortical stroke as lacunar stroke[4] or because CIMT, LVD, and SVD are all associated with hypertension.[5]

The most common imaging biomarker of SVD is white matter lesion (WML) load, but the evidence relating CIMT to WML load is inconsistent.[6,7] This may be because of different inclusion criteria (previous stroke or population-based, wide age range), the multifactorial nature of WML, different rating scales,[6,7] or co-association with some common intermediary factor.[5,8]

Diffusion-tensor magnetic resonance imaging (DT-MRI) may be more sensitive to early effects of SVD. Increased mean diffusivity (<D>) and decreased fractional anisotropy indicate reduced white matter tract integrity.[9] No studies have reported relationships between CIMT and SVD using both WML load and DT-MRI in healthy older people. We investigated the relationship between CIMT, SVD, and LVD (carotid stenosis, vascular history) and common risk factors (blood pressure, diabetes) in older people without stroke within a narrow age range.

Materials and Methods

Subjects

We recruited 115 volunteers from the community by invitation, media appeal, or posters. Exclusion criteria were contraindications to MRI and severe physical/mental illness.[9] One hundred ten completed MRI; 3 scans were excluded because of incidental findings.[9] Lothian Regional Ethics Committee approved the study. All subjects provided informed consent.

CIMT

A trained technician examined the carotid arteries using a 5- to 7-MHz probe in color Doppler mode (Acuson 128xp/10 or Siemens Elegra). An optimal longitudinal, 2-dimensional image of the distal

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Table 1. Descriptive Statistics of 96 Volunteers Without History of Stroke

Variable	N	Mean	SD	Min	Max
Age, y	96	78.4	1.5	75.5	81.5
Right CIMT, mm	96	0.89	0.20	0.50	1.60
Left CIMT, mm	96	0.95	0.22	0.50	1.80
Mean CIMT, mm	96	0.92	0.18	0.50	1.45
ABPI	95	0.91	0.19	0.40	1.63
Frontal <D> ($\times 10^{-6}$ mm^2/sec)	92	835.2	39.8	758.1	994.0
Occipital <D> ($\times 10^{-6}$ mm^2/sec)	92	756.6	40.5	676.7	877.4
Centrum semiovale <D>	93	764.0	40.5	690.0	940.2
Frontal FA	92	0.31	0.03	0.25	0.39
Occipital FA	92	0.42	0.04	0.31	0.55
Centrum semiovale FA	93	0.39	0.06	0.28	0.56
WML load score (Fazekas scale)	0	1	2	3	
PVWML	0	50 (52.1%)	32 (33.3%)	14 (14.6%)	
DWML	8 (8.3%)	69 (71.9%)	13 (13.5%)	6 (6.3%)	

ABPI, ankle–brachial pressure index; CIMT, carotid intima-media thickness (mm); <D>, mean diffusivity; DWML, deep white matter lesion load; FA, fractional anisotropy; PVWML, periventricular white matter lesion load; WML, white matter lesion.

Mean CIMT=[(left+right)/2].

WML load scored from 0 to 3 on the Fazekas scale. Numbers and proportions for each score are given separately for PVWML and DWML.

<D> and FA: n does not equal 96 because of technical issues preventing calculation.

ABPI: n=95 because 1 measurement was not possible because of lymphoedema.

common carotid artery was frozen on screen.[10] Mean CIMT was determined from 3 manual measurements in the far wall of both left and right sides. Maximal carotid artery stenosis was measured using velocity criteria and narrowest residual lumen diameter was measured as a percent of original artery diameter.

Other Vascular Risk Factors

History of vascular disease and risk factors was sought (see Results). Blood pressures at brachial, posterior tibial, and dorsalis pedis arteries were recorded using a Dopplex advanced pocket Doppler VP4 (Huntleigh Diagnostics) on a single occasion after a 2-minute rest. Ankle–brachial pressure index was the lowest leg measurement divided by the higher arm measurement. Blood samples were taken for HbA_{1c}, cholesterol, and triglyceride tests.

MRI and Image Processing

Subjects were scanned on a GE 1.5-T clinical scanner using a previously described protocol including structural MRI (T_2*-weighted gradient-echo, T_1-weighted spin-echo, T_2-weighted, and fluid-attenuated inversion recovery fast spin-echo sequences) and DT-MRI based on single-shot spin-echo echo-planar imaging.[9] An experienced neuroradiologist examined T2*-weighted, T_2-weighted, and fluid-attenuated inversion recovery volumes for infarct or hemorrhage and quantified WML load (Fazekas scale[11]). The <D> and fractional anisotropy volumes were generated and converted into Analyze format (http://www.analyzedirect.com). Regions of interest were placed in normal-appearing frontal and occipital white matter and centrum semiovale using the T_2-weighted echo-planar volumes. All imaging and analyses were blind to all other data.

Statistical Analysis

Relationships between CIMT and markers of LVD, SVD, and intermediary factors were assessed: Spearman ρ for continuous and t test for dichotomous variables. A conservative $P<0.01$ was used. To investigate the influence of potential confounders, ordinal regression (for ordinal outcome variables) or general linear modeling (for continuous variables) was performed.

Results

Of 107 subjects, 11 (10.3%) reported previous stroke or TIA and were excluded from most analyses. Of the remaining 96 (Table 1), 27 (28.1%) were male and mean age was 78.4 (standard deviation, 1.5) years. Thirty-two (33.3%) reported previous cardiovascular disease, 40 (41.7%) reported hypertension, and 6 (6.3%) reported type II diabetes. Seven (7.3%) were current smokers and 42 (43.8%) were former smokers. Another 10 had stroke on MRI (6 infarct, 4 hemorrhage), but these had not caused symptoms and were included in the analyses. There was no gender difference in CIMT ($P=0.52$).

CIMT and LVD Features

There was a significant nonlinear association with carotid stenosis ($\rho=0.28$; $P=0.01$; Table 2).

CIMT and Intermediary Risk Factors

There was a significant association with systolic blood pressure ($\rho=0.34$, $P=0.001$) (Table 2). In multivariate analysis of factors predicting LVD features (% carotid stenosis), there were significant contributions from CIMT (parameter estimate, 4.1; $P<0.001$), age (parameter estimate, 0.44; $P=0.004$), ankle–brachial pressure index (parameter estimate, −3.74; $P=0.001$), cholesterol (parameter estimate, 0.63; $P=0.009$); and history of hypertension (parameter estimate, 1.48; $P<0.001$). No other intermediary risk factors or potential confounders (gender, social class) contributed. The pseudo R^2 was 0.452 ($P<0.001$). The parameter estimate is on an ordered log-odds scale; therefore, the antilog indicates the multiplier change in the odds of moving from one outcome category to another per unit increase, holding covariates constant, ie, a 1-mm increase in CIMT is estimated

Table 2. Relationship Between Carotid Intima-Media Thickness and Large Vessel Disease Features, Intermediary Risk Factors, and Small Vessel Disease Features in 96 Volunteers

Variable	ρ		P
Maximum carotid stenosis	0.28		0.01
Maximum carotid stenosis right	0.19		0.06
Maximum carotid stenosis left	0.26		0.01
ABPI	0.02		0.87
Systolic blood pressure	0.34		0.001
Diastolic blood pressure	0.17		0.09
Total serum cholesterol	0.06		0.67
Triglycerides	−0.11		0.31
HbA1c	0.04		0.69
PVWML	0.05		0.63
DWML	−0.04		0.72
Frontal <D>	−0.02		0.86
Occipital <D>	−0.01		0.93
Centrum semiovale <D>	−0.17		0.11
Frontal FA	−0.22		0.03
Occipital FA	0.04		0.71
Centrum semiovale FA	0.10		0.35
	t	df	P
History of cardiovascular disease	−0.44	94	0.44
Atrial Fibrillation on ECG	0.5	94	0.62
Q wave on ECG	0.32	88	0.75
History of hypertension	−0.38	94	0.14
History of diabetes	−0.41	94	0.68

ABPI, ankle–brachial pressure index; CIMT, carotid intima-media thickness; <D>, mean diffusivity; DWML, deep white matter lesion load; FA, fractional anisotropy; PVWML, periventricular white matter lesion load; WML, white matter lesion.

For continuous data, the relationship with CIMT is investigated using Spearman ρ.

For dichotomous variables, the presence of a significant difference between the CIMT of the 2 groups is investigated using t test.

Large vessel disease features: carotid stenosis, history of cardiovascular disease, and Q wave on ECG.

Intermediary risk factors: ABPI, blood pressure, cholesterol, triglycerides, HbA1c, history of cardiovascular disease, hypertension, or diabetes, and Atrial Fibrillation or Q wave on ECG.

Small vessel disease features: WML load and water diffusion parameters measured in normal-appearing white matter.

to increase the odds of changing carotid stenosis category (20% increase) by a factor of 60.3.

CIMT and SVD Features

There was no consistent significant association between CIMT and WML or DT-MRI parameters (Table 2). Results were similar if those with imaging evidence but no history of stroke were excluded, or if Pearson r was used. Partial correlations correcting for age, gender, social class, blood pressure, BMI, smoking history, and alcohol consumption also showed no significant association with CIMT (data not shown). There was no consistent association between degree of carotid stenosis on either side and SVD (data available from authors). Multivariate analysis did not show any significant influence of intermediary variables or other potential confounders.

Discussion

We found no significant association between CIMT and neuroimaging markers of SVD among 96 men and women aged ≈80 years without history of stroke. There was, however, a significant association between CIMT and LVD (specifically, carotid stenosis) and the intermediary risk factor of systolic blood pressure. In multinomial regression, CIMT remained a predictor of LVD, as were age, history of hypertension, ankle–brachial pressure index, and cholesterol. This is the first study to our knowledge to investigate associations between CIMT and markers of LVD and SVD using DT-MRI at older ages. Carotid stenosis is an overt manifestation of atherosclerosis,[7] and CIMT is an intermediate phenotype for large artery atherosclerosis.[1–3] They, like SVD, are associated with hypertension.[5] Despite small numbers of people with LVD, we found a significant association between CIMT and LVD, adding weight to previous studies suggesting that CIMT is associated with large rather than small vessel damage.[2,3,12]

One strength of this study is that it includes men and women who are older than those in many studies but within a narrow age range (75–81 years). This minimizes the influence of age-dependent variables, such as WMLs, <D>, and fractional anisotropy, which can confound associations in samples with wide age ranges. DT-MRI allows detailed investigation of white matter structure.[9] Potential limitations include the use of volunteers who are typically healthier than the population; our sample had lower rates of cardiovascular disease but similar rates of hypertension, diabetes, and smoking as the population, and it is similar to the samples of other neuroimaging studies including volunteers aged ≈80 years.[13] This may underestimate true associations. Blood pressure was measured on only 1 occasion. A nonsignificant result may be a type II error attributable to the relatively small sample size (with N=96 there is 16.2%, 40.2%, and 85.1% power to detect correlations of 0.1, 0.2, and 0.3 with α=0.05). However, a study of 49 people, aged ≈60 years, using multifractal analysis also failed to find an association between CIMT and white matter structure.[14] The associations between CIMT and LVD may be a type I error attributable to multiple comparisons, although we used a conservative probability value and formal correction is not recommended when variables are intercorrelated and hypotheses are prespecified as here. The methodology used for DT-MRI analyses means that associations between CIMT and DT-MRI parameters may exist in areas in which regions of interest were not placed.

Noninvasive markers to detect those at risk for cerebrovascular disease are attractive, but this study confirms that CIMT is not a useful predictor of SVD in healthy older adults. CIMT and (1) LVD or (2) SVD may represent differences in subject responses to similar risk factors that are perhaps genetically determined.

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Disclosure

None.

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