Large-vessel correlates of cerebral small-vessel disease

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ABSTRACT

Objective: Our aim was to investigate the relationship of carotid structure and function with MRI markers of cerebral ischemic small-vessel disease.

Methods: The study comprised 1,800 participants (aged 72.5 ± 4.1 years, 59.4% women) from the 3C-Dijon Study, a population-based, prospective cohort study, who had undergone quantitative brain MRI and carotid ultrasound. We used multivariable logistic and linear regression adjusted for age, sex, and vascular risk factors.

Results: Presence of carotid plaque and increasing carotid lumen diameter (but not common carotid artery intima-media thickness) were associated with higher prevalence of lacunar infarcts: odds ratio (OR) = 1.60 (95% confidence interval [CI]: 1.09–2.35), $p = 0.02$ and OR = 1.24 (95% CI: 1.02–1.50), $p = 0.03$ (by SD increase). Carotid plaque was also associated with large white matter hyperintensity volume (WMHV) (age-specific top quartile of WMHV distribution): OR = 1.32 (95% CI: 1.04–1.67), $p = 0.02$, independently of vascular risk factors. Increasing Young elastic modulus and higher circumferential wall stress, reflecting augmented carotid stiffness, were associated with increasing WMHV (effect estimate [β] ± standard error: 0.0003 ± 0.0001, $p = 0.024$; β ± standard error: 0.005 ± 0.002, $p = 0.008$). Large WMHV was also associated with increasing Young elastic modulus (OR = 1.22 [95% CI: 1.04–1.42], $p = 0.01$) and with decreasing distensibility coefficient (OR = 0.83 [95% CI: 0.69–0.99], $p = 0.04$), independently of vascular risk factors. Associations of carotid lumen diameter with lacunar infarcts and of carotid stiffness markers with WMHV were independent of carotid plaque.

Conclusions: In addition to and independently of carotid plaque, increasing carotid lumen diameter and markers of carotid stiffness were associated with increasing prevalence of lacunar infarcts and increasing WMHV, respectively. *Neurology*® 2013;80:662-669

GLOSSARY

BI = brain infarct; **CCA** = common carotid artery; **CI** = confidence interval; **IMT** = intima-media thickness; **LI** = lacunar infarct; **L-WMHV** = large white matter hyperintensity volume; **OR** = odds ratio; **SVD** = small-vessel disease; **WMH** = white matter hyperintensity; **WMHV** = white matter hyperintensity volume.

Brain imaging studies have shown that the impact of ischemic brain injury, a major cause of disability, dementia, and mortality in adults,[1] extends much beyond that of acute clinical events such as stroke. Vascular lesions, including MRI-defined brain infarcts (BIs) and white matter hyperintensities (WMH), are frequently observed in older community-dwelling individuals. The prevalence of BIs ranges between 8% and 28%[2,3]; most are small and located in subcortical brain regions, referred to as lacunar infarcts (LIs). WMH volume (WMHV) is estimated between 1.5 and >10 cm³ in population-based cohorts on average,[4] and >90% of subjects aged 80 years and older have some degree of white matter damage.[5] LIs and WMH are believed to result mostly from cerebral ischemic small-vessel disease (SVD),[6] and predict an increased risk of stroke, dementia, and death.[5]

Supplemental data at www.neurology.org

Age and high blood pressure are major risk factors for MRI markers of ischemic SVD,[1,5] but underlying mechanisms are not fully understood. Although an association of increasing carotid intima-media thickness (IMT) and number or characteristics of carotid plaques with LI and WMHV was suggested, results are partly controversial.[7–9] Besides, little is known about the relationship of large-artery geometry and stiffness with cerebral ischemic SVD.

We aimed to examine the relationship of ultrasound markers for carotid structure and function with MRI markers of cerebral ischemic SVD in a large community-based sample. This could improve our understanding of the pathophysiology underlying this highly prevalent cerebrovascular disorder and guide clinicians in the workup and management of patients at risk of cerebrovascular disease.

METHODS Population and study design. The 3C-Dijon Study is a prospective cohort study whose design has been described in detail elsewhere.[10,11] Briefly, 4,931 noninstitutionalized persons aged 65 years and older were recruited from the electoral rolls of Dijon, France, between March 1999 and March 2001. Participants enrolled between June 1999 and September 2000, younger than 80 years, and who were able to come to the examination center (n = 2,763) were invited to undergo a brain MRI. Although 2,285 subjects agreed to participate, because of financial limitations, only 1,924 MRI scans were performed. A carotid ultrasound examination with evaluation of carotid structure was proposed to all participants younger than 85 years (n = 4,580) who were able to come to the examination center. Because of logistic concerns, this examination was not proposed during the last 6 months of subject recruitment and was finally performed on 3,323 participants. Estimation of carotid wall mechanics (carotid function) was provided by a special protocol introduced between December 1999 and December 2000, and thus proposed to the 2,391 subjects who underwent carotid ultrasound examination during this period. Carotid function could be measured in 76.5% of them (n = 1,830). In total, 1,800 participants had both measures of carotid structure and a brain MRI scan with evaluation of lacunar BIs (1,742 with quantitative WMHV measurement); 912 participants had both measures of carotid function and a brain MRI scan with evaluation of BIs (879 with quantitative WMHV measurement). Among participants with brain MRI measurements, those with measures for carotid structure were slightly older than participants with measures for both carotid structure and function, but had similar vascular risk factor profiles (table e-1 on the *Neurology*® Web site at www.neurology.org).

Standard protocol approvals, registrations, and patient consents. The Ethics Committee of Kremlin-Bicêtre University Hospital approved the study protocol, and each participant signed an informed consent.

Brain MRI. MRI acquisition was performed on a 1.5-T Magnetom scanner (Siemens, Erlangen, Germany) using T1-weighted, T2-weighted, and proton density–weighted sequences. A fast, multislice, double-echo, T2-weighted, 2-dimensional axial acquisition was used, with 4-mm-thick slices, and 0.4 mm between slice spacing. Raw data

were transferred for analysis and storage to the MRI study center (Department of Neurofunctional Imaging, Caen). BIs were rated on T1-weighted, T2-weighted, and proton density–weighted images by a single rater, and defined as focal lesions ≥3 mm in diameter, with the same signal characteristics as CSF on all sequences.[12] They were discriminated from dilated Virchow-Robin spaces using multiplanar reformatting: lesions with a typical vascular shape and following the orientation of perforating vessels were regarded as dilated Virchow-Robin spaces. LIs were defined as BIs of 3 to 15 mm in size, located in the basal ganglia or in the white matter. Subjects with a non-lacunar BI were excluded from analyses of LIs. Fully automated image-processing software was developed to detect, measure, and localize WMH.[13]

Carotid ultrasound examination. *Carotid structure.* Ultrasound measurements were performed with the B-mode system (Ultramark 9 High Definition Imaging; Advanced Technology Laboratories) using 5- to 10-MHz sounding, according to a standardized scanning protocol, with standardized central reading at Broussais Hospital, Paris.[14] Plaque was defined as localized echo structures encroaching into the vessel lumen for which the distance between the media-adventitia interface and internal side of the lesion was ≥1 mm, on common carotid arteries (CCAs), carotid bifurcations, and internal carotid arteries.[14] CCA-IMT was measured at a site free of any discrete plaque along a 10-mm-long segment on the far wall of the CCA, as the distance between lumen-intima and media-adventitia interfaces. On average, 75 measurements were automatically performed on each image and each side. The mean of right and left mean CCA-IMT values was used. Systolic and diastolic CCA lumen diameter was determined for each cardiac cycle and defined as the average of distances between leading edges of far and near wall lumen–intima interfaces along ≥0.5 cm of length using a computerized validated program.[14] Diastolic CCA lumen diameter was used for analyses (referred to as carotid lumen diameter throughout the text).

Carotid function. Ultrasound markers of carotid function are useful surrogates to assess large-artery stiffness. We used the following 4 markers to evaluate elastic properties of the carotid artery (e-Methods): carotid distension, representing the relative stroke change of diameter; cross-sectional distensibility coefficient, determined by stroke change of cross-sectional area relative to pulse pressure,[15] which evaluates elastic properties of large arteries as hollow structures[16]; Young elastic modulus, representing elastic properties of arterial wall material[17]; circumferential wall stress, corresponding to tensile stress applied in the tangential direction to the arterial wall to enlarge the lumen.[16] We used brachial oscillometric blood pressure measured during carotid ultrasonography in calculations. Decreasing carotid distension and distensibility coefficient and increasing Young elastic modulus and circumferential wall stress reflect increasing carotid stiffness.

Covariates. For covariate definitions, see e-Methods.

Statistics. Because WMHV and total white matter volume are highly correlated, we studied WMHV as the ratio of total WMHV to total white matter volume. Large WMHV (L-WMHV) was defined as the top age-specific quartile of WMHV distribution (by 5-year age categories). WMHV and triglyceride levels were log-transformed, as they were not normally distributed. We tested the association of vascular risk factors with LIs and L-WMHV using a χ^2 test for categorical variables and Student t test for continuous variables.

In our primary analysis, we examined the relationship of MRI markers of cerebral ischemic SVD (WMHV, L-WMHV, LIs) with markers of carotid structure (carotid plaque, CCA-IMT, carotid lumen diameter) and function (carotid distension, cross-sectional distensibility coefficient, circumferential wall stress, Young elastic modulus) using a multivariable linear regression for continuous outcomes

and multivariable logistic regression for dichotomous outcomes. We first adjusted for age and sex, then additionally for vascular risk factors associated with BIs or WMH burden ($p < 0.05$). Odds ratios are expressed by SD increase for continuous independent variables.

To assess the robustness of our findings, we verified whether associations were maintained after adjusting for brachial pulse pressure and antihypertensive drugs instead of hypertension, and after excluding participants with prevalent stroke (n = 42). We also tested whether findings were similar in subgroups stratified by hypertension, body surface area (which is highly correlated with vessel dimensions), age, and sex. Body surface area and age were dichotomized according to the sex-specific mean. To evaluate whether associations with carotid lumen diameter and carotid stiffness markers were independent of carotid plaque, we ran analyses including carotid plaque in the model in addition to carotid lumen diameter or carotid function parameters. We also performed a forward stepwise logistic regression with $p = 0.10$ as a significance threshold for entering into and staying in the model, to evaluate which parameters best predicted MRI markers of cerebral ischemic SVD. To examine whether markers of carotid structure are associated with severity of cerebral ischemic SVD, we created an "SVD-severity" score ranging from 0 to 2: 0 for participants without LI and without L-WMHV; 1 for participants with ≥1 LI or L-WMHV; 2 for participants with ≥1 LI and L-WMHV. We used multinomial logistic regression (generalized logit model), relating each carotid marker to this score.

Analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS Characteristics of the study population are detailed in table 1. Among the 1,800 individuals studied, 150 (8.3%) had >1 LI and mean WMHV was 5.5 ± 4.9 cm³. Male sex, increasing age, history of cardiovascular disease, hypertension, and triglycerides were significantly associated with L-WMHV and LIs; diabetes and body mass index were significantly associated with L-WMHV (table 2).

Carotid structure and MRI markers of cerebral ischemic SVD. Carotid plaque and increasing carotid lumen diameter were significantly associated with LIs, L-WMHV, and increasing WMHV (table 3). After adjustment for vascular risk factors, these relationships were attenuated, but associations of carotid plaque with LIs, increasing WMHV and L-WMHV, and of carotid lumen diameter with LIs remained significant (table 3). Associations were similar when using brachial pulse pressure and antihypertensive treatment as covariates instead of hypertension, after exclusion of participants with prevalent stroke (data not shown), and in subgroups stratified on sex, body surface area, age, and hypertension (table e-2). Moreover, when we included both carotid plaque and carotid lumen diameter in the same model, associations of each with LIs, and of carotid plaque with L-WMHV, remained significant (table 3). In a forward stepwise logistic regression (table 4) with LIs as an outcome, carotid plaque, carotid lumen diameter, sex, age, hypertension, and history of cardiovascular disease were retained in the model. For L-WMHV, carotid plaque, carotid lumen diameter, hypertension, diabetes, and history of cardiovascular disease were

Table 1	Principal characteristics of the study population (n = 1,800)[a]
Risk factors	
Age, y	72.5 ± 4.1
Men	721 (40.6)
Body mass index, kg/m²	25.5 ± 3.9
Hypertension[b]	1,385 (76.9)
Systolic blood pressure, mm Hg	143.7 ± 21.9
Diastolic blood pressure, mm Hg	81.5 ± 10.7
Diabetes mellitus[c]	156 (8.7)
Current smokers	104 (5.8)
Hypercholesterolemia[d]	1,012 (56.5)
History of cardiovascular disease[e]	108 (6.0)
Carotid structure	
CCA-IMT, mm	0.68 ± 0.10
Carotid lumen diameter, mm	6.08 ± 0.80
Carotid plaque	872 (48.4)
Carotid function[f]	
Distension, %	9.3 ± 2.5
Distensibility coefficient, kPa⁻¹	0.025 ± 0.009
Circumferential wall stress, kPa	58.9 ± 12.5
Young elastic modulus, kPa	403.7 ± 190.9

Abbreviation: CCA-IMT = common carotid artery intima-media thickness.
[a] Data are mean ± SD or n (%).
[b] Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive drugs.
[c] Fasting blood glucose ≥7 mmol/L or use of antidiabetic drugs.
[d] Total cholesterol ≥6.2 mmol/L or use of lipid-lowering drugs.
[e] History of stroke, myocardial infarction, angina pectoris, or heart failure.
[f] n = 912.

retained (table 4). We observed a graded association of carotid plaque and increasing carotid lumen diameter with increasing SVD severity (table 5). CCA-IMT was not associated with MRI markers of cerebral ischemic SVD. Associations were similar in participants who underwent evaluation of carotid function and those who did not (table e-3).

Carotid function and MRI markers of cerebral ischemic SVD. Increasing Young elastic modulus and circumferential wall stress, as well as decreasing distension and distensibility coefficient, were associated with increasing WMHV and prevalence of L-WMHV (table 3). After adjustment for vascular risk factors, associations remained significant for Young elastic modulus, circumferential wall stress, and distensibility coefficient. These associations also persisted when additionally adjusting for carotid plaque (table 3) and when using brachial pulse pressure and antihypertensive treatment as a covariate instead of hypertension (data not shown).

Table 2 Vascular risk factors according to presence or absence of brain MRI markers of ischemic SVD[a]

	Lacunar infarcts				L-WMHV			
	Yes (n = 150)	No (n = 1,650)	p	p$_{adj}$[b]	Yes (n = 430)	No (n = 1,312)	p	p$_{adj}$[b]
Age, y	73.9 ± 4.2	72.3 ± 4.1	<0.0001		73.0 ± 4.2	72.7 ± 4.1	0.13	
Men	92 (61.3)	629 (38.1)	<0.0001		196 (46.1)	492 (37.3)	<0.0001	
Body mass index, kg/m²	26.2 ± 3.6	25.4 ± 3.9	0.025	0.11	25.9 ± 3.9	25.2 ± 3.7	0.003	0.009
Hypertension[c]	136 (90.7)	1,249 (75.7)	<0.0001	0.002	365 (84.9)	977 (74.5)	<0.0001	<0.0001
Systolic blood pressure, mm Hg	150.9 ± 25.6	143.6 ± 21.4	<0.0001	0.002	147.5 ± 22.2	142.3 ± 21.7	<0.0001	0.0002
Diastolic blood pressure, mm Hg	83.9 ± 11.9	81.5 ± 10.5	<0.0001	0.006	83.7 ± 10.8	80.6 ± 10.5	<0.0001	<0.0001
Pulse pressure, mm Hg	67.9 ± 18.3	63.4 ± 16.6	0.002	0.26	63.4 ± 17.0	61.7 ± 16.4	0.018	0.047
Antihypertensive treatment	87 (58.0)	685 (41.5)	<0.0001	0.003	238 (54.6)	515 (39.4)	<0.0001	<0.0001
Diabetes mellitus[d]	17 (11.4)	139 (8.5)	0.29	0.97	52 (12.4)	96 (7.4)	0.002	0.005
Current smokers	9 (6)	95 (5.8)	0.014	0.95	31 (7.2)	65 (5.0)	0.055	0.31
HDL cholesterol, mmol/L	1.6 ± 0.42	1.7 ± 0.4	0.002	0.65	1.6 ± 0.4	1.7 ± 0.4	0.14	0.56
LDL cholesterol, mmol/L	3.5 ± 0.8	3.6 ± 0.8	0.60	0.50	3.5 ± 0.9	3.6 ± 0.8	0.12	0.18
Triglycerides, mmol/L	1.4 ± 0.7	1.2 ± 0.5	0.001	0.006	1.3 ± 0.6	1.2 ± 0.6	0.004	0.008
History of cardiovascular disease[e]	26 (17.3)	82 (5.0)	<0.0001	<0.0001	41 (9.5)	71 (5.4)	0.0025	0.0389

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; L-WMHV: large white matter hyperintensity volume (age-specific top quartile); SVD = small-vessel disease.

[a] Data are mean ± SD or n (%).

[b] Adjusted for age and sex.

[c] Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive drugs.

[d] Fasting blood glucose ≥7 mmol/L or use of antidiabetic drugs.

[e] History of myocardial infarction, angina pectoris, or heart failure.

Subgroup analyses stratified by age, sex, body surface area, and hypertension yielded consistent results (table e-2). LIs were not associated with carotid function parameters after adjustment for vascular risk factors (table 3).

DISCUSSION In a large sample of elderly community participants, carotid plaque was associated with a higher prevalence of LIs and increasing WMHV. Independently of carotid plaque, larger carotid lumen diameter predicted an increased prevalence of LIs, whereas functional markers of carotid stiffness were associated with increasing WMH burden. These associations were attenuated but maintained after adjustment for vascular risk factors. Cerebral ischemic SVD was not associated with CCA-IMT.

The association of LIs with carotid plaque is in agreement with the literature.[18,19] Previous publications also described an association among carotid stenosis, number or characteristics of carotid plaque, and WMHV.[7,9,20] In the present dataset, we observed an association of carotid plaque with WMHV and L-WMHV, even after accounting for vascular risk factors. Mechanisms underlying the association of carotid plaque with cerebral ischemic SVD are unclear. Factors that may interfere with cerebral blood flow such as concomitant micro-atheroma at the origin of perforator arteries may have a role.[21] Cerebral emboli originating from ruptured or ulcerated carotid plaque could also be involved, although they may not be a major contributor in a population-based setting.[9] Carotid plaque may also reflect the overall effect of uncontrolled vascular risk factors, or lifetime exposure to these, better than each vascular risk factor taken individually.

Interestingly, carotid lumen diameter, another much less-studied marker of carotid structure, was also associated with increased prevalence of LIs, and to a lesser extent WMHV. Arterial dilatation may act as a compensatory mechanism to counteract an increase in stiffness and thickness of the arterial wall and maintain arterial compliance in the normal values.[22–24] The fact that association of increasing carotid lumen diameter with LIs was maintained after adjusting for carotid plaque, and that we did not observe any association of CCA-IMT with cerebral ischemic SVD, suggest that this relationship was not driven only by carotid atherosclerosis and thickening. The cellular and molecular mechanisms of diameter enlargement are speculative, but may involve an excessive extracellular matrix turnover, a lack of vascular smooth muscle cell proliferation, or apoptosis,[25] which could occur not only in the carotid artery, but also concomitantly in small cerebral arteries.

The absence of association of CCA-IMT with MRI markers of cerebral ischemic SVD is in contrast with results from other population-based studies,[8,9] although some associations were observed primarily with internal

Table 3 Association of carotid structure and function with MRI markers of cerebral ischemic SVD

	Lacunar infarcts		WMHV[a]		L-WMHV	
	OR (95% CI)	p	β ± SE	p	OR (95% CI)	p
Adjusted for age and sex						
Carotid structure	n = 1,800		n = 1,742		n = 1,742	
CCA-IMT	1.06 (0.90–1.25)	0.49	0.062 ± 0.147	0.67	1.04 (0.93–1.16)	0.48
Carotid lumen diameter	1.36 (1.14–1.62)	0.0005	0.070 ± 0.023	0.002	1.21 (1.07–1.36)	0.002
Carotid plaque	1.88 (1.31–2.70)	0.0006	0.092 ± 0.031	0.003	1.48 (1.19–1.86)	0.0005
Carotid function	n = 912		n = 879		n = 879	
Distension	1.08 (0.84–1.37)	0.56	−0.018 ± 0.009	0.039	0.86 (0.74–1.01)	0.066
Distensibility coefficient	0.93 (0.71–1.21)	0.56	−4.513 ± 2.321	0.052	0.78 (0.65–0.93)	0.005
Circumferential wall stress	1.16 (0.91–1.48)	0.22	0.006 ± 0.002	0.002	1.27 (1.08–1.49)	0.003
Young elastic modulus	1.20 (1.00–1.45)	0.053	0.0003 ± 0.0001	0.011	1.33 (1.13–1.57)	0.0007
Adjusted for age, sex, and vascular risk factors[b]						
Carotid structure	n = 1,800		n = 1,742		n = 1,742	
CCA-IMT	1.04 (0.88–1.23)	0.64	−0.044 ± 0.148	0.76	1.01 (0.90–1.13)	0.92
Carotid lumen diameter	1.25 (1.04–1.50)	0.019	0.040 ± 0.023	0.084	1.12 (0.99–1.27)	0.078
Carotid plaque	1.62 (1.11–2.35)	0.012	0.062 ± 0.031	0.048	1.37 (1.08–1.72)	0.008
Carotid function	n = 912		n = 879		n = 879	
Distension	1.12 (0.87–1.45)	0.38	−0.017 ± 0.009	0.052	0.85 (0.72–1.00)	0.049
Distensibility coefficient	1.04 (0.79–1.35)	0.79	−3.629 ± 2.369	0.13	0.81 (0.67–0.97)	0.021
Circumferential wall stress	1.03 (0.80–1.34)	0.79	0.005 ± 0.002	0.008	1.19 (1.01–1.41)	0.035
Young elastic modulus	1.13 (0.93–1.37)	0.21	0.0002 ± 0.0001	0.032	1.28 (1.08–1.51)	0.004
Adjusted for age, sex, vascular risk factors,[b] and carotid plaque[c]						
Carotid structure	n = 1,800		n = 1,742		n = 1,742	
CCA-IMT	1.01 (0.85–1.20)	0.86	−0.075 ± 0.149	0.61	0.99 (0.88–1.11)	0.87
Carotid lumen diameter	1.22 (1.01–1.47)	0.035	0.037 ± 0.023	0.12	1.10 (0.97–1.25)	0.13
Carotid plaque	1.60 (1.09–2.34)	0.015	0.057 ± 0.032	0.076	1.33 (1.05–1.68)	0.016
Carotid function	n = 912		n = 879		n = 879	
Distension	1.10 (0.85–1.42)	0.45	−0.018 ± 0.009	0.040	0.84 (0.71–0.99)	0.037
Distensibility coefficient	1.04 (0.80–1.36)	0.76	−3.470 ± 2.368	0.14	0.81 (0.68–0.97)	0.025
Circumferential wall stress	1.05 (0.81–1.35)	0.73	0.005 ± 0.002	0.006	1.20 (1.02–1.42)	0.028
Young elastic modulus	1.12 (0.92–1.36)	0.25	0.0002 ± 0.0001	0.037	1.27 (1.08–1.51)	0.005

Abbreviations: CCA-IMT = common carotid artery intima-media thickness; CI = confidence interval; L-WMHV = large white matter hyperintensity volume (age-specific top quartile); OR = odds ratio (per SD increase); SE = standard error; SVD = small-vessel disease; WMHV = white matter hyperintensity volume.

[a] Log-transformed ratio of WMHV over total white matter volume.

[b] Body mass index, hypertension, smoking, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, log-transformed triglycerides level, lipid-lowering drugs, diabetes mellitus, and history of cardiovascular disease.

[c] Except for the association with carotid plaque, which was adjusted for carotid lumen diameter.

carotid artery IMT.[8] In the 3C-Dijon Study, CCA-IMT was measured at a site free of plaque,[26] whereas plaques were included in the measurement of carotid IMT in other studies.[8,9] In these studies, IMT probably reflects more advanced atherosclerosis, whereas increased IMT at a site free of plaque can also correspond to nonatherosclerotic thickening, such as an adaptive response to altered shear stress or circumferential wall stress.[27]

Several markers of carotid stiffness were associated with increasing WMH burden, independently of vascular risk factors and carotid plaque. The relationship of pulse wave velocity, a marker of aortic stiffness, with MRI markers of ischemic brain injury was recently assessed, in relatively small samples.[19,28–32] After accounting for vascular risk factors, pulse wave velocity was consistently associated with WMH burden,[30–32]

Table 4 Association of carotid structure and vascular risk factors with brain MRI markers of cerebral ischemic SVD using a forward stepwise logistic regression[a]

	Lacunar infarcts		L-WMHV	
	OR (95% CI)	p	OR (95% CI)	p
Carotid plaque	1.58 (1.08–2.30)	0.017	1.32 (1.05–1.67)	0.007
Carotid lumen diameter	1.23 (1.03–1.48)	0.024	1.14 (1.02–1.28)	0.002
Male sex	1.73 (1.17–2.58)	0.006		
Age	1.06 (1.02–1.11)	0.004		
Hypertension	2.12 (1.87–3.80)	0.011	1.65 (1.22–2.23)	<0.0001
History of cardiovascular disease	2.71 (1.63–4.52)	0.0001	1.52 (1.00–2.31)	0.048
Diabetes mellitus			1.46 (1.01–2.12)	0.028

Abbreviations: CI = confidence interval; L-WMHV = large white matter hyperintensity volume (age-specific top quartile); OR = odds ratio (per SD increase); SVD = small-vessel disease.
[a] Independent variables included in the analysis were carotid plaque, carotid lumen diameter, and vascular risk factors associated with brain infarcts or L-WMHV at $p < 0.05$ in a univariate analysis; $p = 0.10$ was used as a significance threshold for entering into and staying in the model; results are shown only for variables retained in the final model.

whereas associations with MRI-defined BIs were controversial.[19,28,30–32] Our results lend further support to an association of large-artery stiffness with WMH burden, and extend the findings to markers of carotid stiffness, additionally demonstrating that this association is at least in part independent of carotid atherosclerosis. Markers of carotid stiffness were not associated with LIs in our sample, suggesting that carotid stiffness may have an important role in chronic hypoperfusion but not complete infarction in the territory of small arteries.[33]

The mechanisms underlying the association between carotid stiffness and WMH burden are speculative. Large-artery stiffening is an important feature of arterial aging, associated with increased risk of cardiovascular events,[34] but also with reduced glomerular filtration rate and cognitive impairment.[35–37] In contrast with other organs, kidney and brain are continually and passively perfused at high-volume flow throughout systole and diastole.[38] This exposes small renal and cerebral vessels to highly pulsatile pressure and flow, eventually leading to hypertrophic remodeling and rarefaction of small arteries, causing chronic ischemia.[39] Increase in vasomotor tone of small arteries and capillary rarefaction could in turn promote large-artery stiffening by increasing the amplitude of the reflected wave, leading to a vicious circle. Other mechanisms could include structural damage at the molecular and cellular level, occurring simultaneously in the wall of large and small arteries, such as increased extracellular matrix turnover, impaired vascular smooth muscle cell proliferation, and apoptosis,[25] thus promoting ischemia, in the territory of small cerebral arteries. Interestingly, increasing circumferential wall stress was also associated with WMHV after adjustment for pulse pressure, suggesting a defect of arterial wall thickening, unable to normalize wall stress.

Strengths of our study include the large sample size in a population-based setting, the quantitative measurement of brain MRI markers, and simultaneous assessment of carotid structure and function. Although other studies have examined the relationship of large-artery atherosclerosis and stiffness with MRI markers of vascular brain injury, to our knowledge, none have simultaneously assessed their impact on MRI markers of ischemic SVD. Moreover, most studies have used markers of aortic stiffness. Carotid lumen diameter and carotid stiffness markers can be measured noninvasively, simultaneously with carotid plaque, and our data suggest that they could predict cerebral ischemic SVD above and beyond the presence of carotid plaque.

Table 5 Association of carotid structure with increasing severity of cerebral ischemic SVD

	Lacunar infarcts *or* L-WMHV vs none		Lacunar infarcts *and* L-WMHV vs none		
	OR$_1$ (95% CI)[a] n = 411/1,701	p	OR$_2$ (95% CI)[b] n = 71/1,701	p	Global p
Adjusted for age and sex					
CCA-IMT	1.07 (0.95–1.20)	0.26	1.01 (0.80–1.28)	0.90	0.53
Carotid lumen diameter	1.19 (1.05–1.35)	0.005	1.49 (1.17–1.90)	0.001	0.0004
Carotid plaque	1.40 (1.12–1.76)	0.004	2.57 (1.50–4.41)	0.0006	0.0001
Adjusted for age, sex, and vascular risk factors[c]					
CCA-IMT	1.04 (0.93–1.17)	0.50	0.98 (0.76–1.24)	0.85	0.76
Carotid lumen diameter	1.08 (0.94–1.23)	0.26	1.37 (1.06–1.77)	0.017	0.043
Carotid plaque	1.31 (1.03–1.66)	0.026	2.09 (1.20–3.65)	0.009	0.005

Abbreviations: CCA-IMT = common carotid artery intima-media thickness; CI = confidence interval; L-WMHV = large white matter hyperintensity volume (age-specific top quartile); OR = odds ratio (per SD increase); SVD = small-vessel disease.
[a] OR$_1$: comparing participants with lacunar infarcts or L-WMHV but not both to reference group.
[b] OR$_2$: comparing participants with lacunar infarcts and L-WMHV to reference group.
[c] Body mass index, hypertension, smoking, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, log-transformed triglycerides level, lipid-lowering drugs, diabetes mellitus, and history of cardiovascular disease.

Although the sample with measures of carotid function was smaller than the sample with measures of carotid structure, eligibility of participants for the substudy on carotid function depended only on the period of recruitment, thus a selection bias is unlikely. We used brachial blood pressure to calculate markers of carotid stiffness; however, because central and peripheral blood pressures converge with aging, this is unlikely to have influenced our findings substantially.[25]

The present findings, if confirmed, have 2 major implications. First, they suggest a strong relationship between large-artery aging and cerebral ischemic SVD, markers of carotid structure and function being associated with different components of SVD. This information could be used to optimize prevention strategies for cerebral SVD and their consequences on the risk of stroke and dementia. For instance, it might be of interest to explore whether antihypertensive treatments reducing primarily systolic blood pressure through a "de-stiffening" strategy are more effective than other antihypertensive protocols in preventing progression of WMH burden.[40] Second, our findings imply that markers of carotid structure and function could be implemented as a screening tool to triage patients at high risk of cerebral ischemic SVD, requiring further, more costly investigations, including brain MRI.

AUTHOR CONTRIBUTIONS

Dr. Marion Brisset: drafting the manuscript, statistical analysis, analysis and interpretation. Dr. Pierre Boutouyrie: critical revision of the manuscript for important intellectual content, study design, acquisition of data. Dr. Fernando Pico: critical revision of the manuscript for important intellectual content. Dr. Yicheng Zhu: critical revision of the manuscript for important intellectual content, acquisition of data. Dr. Mahmoud Zureik: critical revision of the manuscript for important intellectual content. Mrs. Sabrina Schilling: critical revision of the manuscript for important intellectual content, analysis and interpretation. Dr. Carole Dufouil and Dr. Bernard Mazoyer: critical revision of the manuscript for important intellectual content, acquisition of data. Dr. Stéphane Laurent: critical revision of the manuscript for important intellectual content, study design, acquisition of data. Dr. Christophe Tzourio: critical revision of the manuscript for important intellectual content, study design, acquisition of data, study supervision or coordination, obtaining funding. Dr. Stéphanie Debette: drafting/revising the manuscript for content, statistical analysis, study supervision or coordination.

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