Vascular Structure and Function Is Correlated to Cognitive Performance and White Matter Hyperintensities in Older Hypertensive Patients With Subjective Memory Complaints

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Background and Purpose—Arterial stiffening and thickening and endothelial dysfunction may be associated with cognitive decline or white matter hyperintensities (WMH) independently of blood pressure level. We aimed to investigate, using an integrative approach, the relative contributions of structural and functional vascular factors to the degree of cognitive impairment (primary outcome) and the severity of WMH (secondary outcome) in elderly hypertensive patients with subjective memory complaints, a group prone to dementia.

Methods—A prospective, dedicated, cross-sectional population of 198 elderly hypertensive patients (mean age 69.3 ± 6.2 years) with subjective memory complaints underwent a full set of cognitive function assessments, brain MRI with semiquantification of WMH, carotid ultrasonography, carotid–femoral pulse wave velocity, brachial endothelial function, and plasma von Willebrand Factor measurements.

Results—After adjustment for the usual cardiovascular risk factors, increased arterial stiffness (as assessed by pulse wave velocity) was significantly and independently associated with memory impairment in men. The severity of WMH was independently associated with increased carotid intima media thickness and stiffness (as assessed by augmentation index) as well as with increased age and plasma levels of von Willebrand Factor, a biomarker of endothelial dysfunction.

Conclusions—Our data suggest that vascular abnormalities, independently of blood pressure levels, may play a role in the setting of subjective memory complaints as well as of WMH in elderly hypertensive patients. Arterial thickness and stiffness as well as endothelial function should be assessed simultaneously and may represent additional targets for the prevention of subjective memory complaints and WMH. (Stroke. 2009;40:1229-1236.)

Key Words: aging ■ arterial stiffness ■ cognitive impairment ■ hypertension ■ leukoaraiosis

Dementia prevalence in developed countries is approximately 1.5% in the population >65 years and doubles every 4 years to reach approximately 30% at 80 years,1 making disorders of cognition a priority for healthcare and social care services. Alzheimer disease (AD) is responsible for 50% to 60% of dementia cases, whereas 30% of patients have vascular dementia (VaD), and 10% to 20% have a mixed form of dementia.2 There is an extensive overlap between AD and VaD, because it has been estimated that more than one third of AD cases display cerebrovascular alterations and that approximately one third of patients with diagnosed vascular dementia will have AD at autopsy.3 AD and VaD indeed share common risk factors such as hypertension, smoking, and diabetes.2 It has been suggested that atherosclerosis may cause localized or global brain hypoperfusion, which may lead to AD, white matter lesions (WML), or both.2 In a population-based setting, the presence of carotid plaques and increased carotid wall thickness4–5 were found to be associated with lower cognitive performances. Increased arterial stiffness (AS), another marker of subclinical vascular structural changes, was reported to be associated with impaired cognitive function in a cross-sectional population-based setting,6 and in elderly patients either with VaD7 or AD, mild cognitive impairment (MCI),8 and memory loss.9,10 Other

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studies have reported associations between WML and endothelial dysfunction in a community-based population setting and in older adults with cardiovascular disease and between WML and carotid intima media thickness (IMT). Therefore, beyond blood pressure (BP), AS and thickening as well as endothelial dysfunction have been separately associated with cognitive decline or white matter hyperintensities (WMH) in few individual large studies, in unselected populations as well as in patients with various cardiovascular risk profiles. AS and thickening and endothelial dysfunction are integrative phenotypes influenced by a number of risk factors, including blood pressure, which have been used extensively in previous works as strong intermediate phenotypes correlated to cardiovascular outcomes.

The aim of our study was to investigate the relative contribution of AS and thickening and endothelial dysfunction to cognitive decline (primary end point) and WMH (secondary end point) using an integrative approach with comprehensive and concomitant assessments of arterial structure and function in a selected population at high risk of vascular remodeling and/or dementia, ie, elderly hypertensive patients with various levels of subjective memory complaints (SMC), including patients with documented MCI but no dementia.

Materials and Methods

Subjects
The study was a cross-sectional, single-center study. Patients were recruited between September 2003 and August 2005 by local press advertisements or referral by general practitioners from an investigator network of the Inserm Clinical Investigation Centre. Inclusion criteria were: men and women aged 60 to 85 years with a history of hypertension, lasting more than 1 year, and treated at the time of inclusion and function in a selected population at high risk of vascular remodeling and/or dementia.

Exclusion criteria were known secondary hypertension, severe hypertension (systolic BP [SBP] >200 mm Hg or diastolic BP [DBP] >120 mm Hg) or malignant hypertension, severe hypotension, serum creatinine >2.5 mg/dL (ie, 221 μmol/L), transaminases over twice the upper normal laboratory value, body mass index >40 kg/m², history of stroke, heart failure New York Heart Association class III, cancer or systemic diseases, history of nervous system disorders, known dementia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria), suspicion of dementia (Mini Mental State Examination score ≤24 for lower education level and ≤26 for high education level), suspicion of depression (Geriatric Depression Scale >10), and history of alcohol or drug abuse, treatments influencing cognitive efficiency evaluation (narcoleptics, antiepileptic or anti-psychotic drugs). The study was approved by the local research ethics committee and all patients signed an informed consent form.

The clinical evaluation included history recording and a general and neurological examination. Education level was classified into 3 categories: low (eg, primary education), medium (eg, lower-level general education, intermediate-level general education), and high (eg, higher-level general education and university). Supine SBP and DBP were measured after at least 10 minutes of rest, on the left arm, using a validated electronic device (DINAMAP 400Pro). BP was measured 3 times, and the average of these 3 measurements was used for statistical analyses. Ambulatory BP measurements (ABPM)/24 hours (SpaceLabs) were also recorded.

Cognitive status was established by a set of psychometric tests. First, the Cognitive Difficulties Scale of McNair was performed by self-evaluation (inclusion criteria). Then the Geriatric Depression Scale, a self-report scale, was completed. A global cognitive assessment was based on the Mini Mental State Examination. A validated and comprehensive battery of neuropsychological tests was performed by trained psychologists, including immediate and delayed memory and language (free and cued recall) assessed by the Grober-Buchske test, visuoperceptual and visuospatial capacities by the Benton Visual Retention Test, praxies by the Praxies scale, and executive function and long-term verbal memory by the Verbal Fluency Test. Composite scores were calculated for memory function (real memory score, including 2 components from the Grober-Buchske test: free [episodic memory] and cued [semantic memory] recalls), verbal fluency (which describes language lexical fluidity and includes 4 tests), and visual memory capacity (visual memory score, defining raw visual memory and errors with 2 tests). Each composite score was made by transforming individual test scores into standardized Z-scores (Z-score=raw score-mean test score/SD).

Magnetic Resonance Imaging
Brain MRI at 1.5 T (Signal General Electric; GE MRS) was performed in the axial and sagittal planes with the slice thickness of 5 mm. WML grading was performed using T2-weighted axial images. Each MRI was screened initially by a neuroradiologist to rule out stroke or the presence of 3 or more lacunar infarcts (exclusion criteria) and other possible causes of gait imbalance. The grading was performed blind by one experienced neuroradiologist using the scale of Fazekas and Schmidt, which accounts separately for periventricular corps and deep white matter corps (subcortical). The deep white matter corps rating accounts separately for the number and extent of lesions. The number is given as 0 for no lesion, 1 for one to 4 lesions, 2 for 5 to 9 lesions, and 3 for ≥10 lesions. Deep white matter corps extent is given as 0 for no lesion, 1 for punctuate foci, 2 for beginning confluent foci, and 3 for confluent deep white matter corps. Periventricular corps is scored as 1 for caps or pencil-thin lining, 2 for smooth halo, and 3 for irregular periventricular corps extending into deep white matter. The Fazekas score represents the sum of deep white matter corps and periventricular corps divided into 3 groups of increasing severity (ie, 0 to 1, 2 to 3, 4 to 6).

Among rating scales, the Fazekas score presents the advantage of displaying the highest interrater agreements and correlation with volumetric measurements.

Blood and Urine Sampling
Total serum cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, HbA1C, fasting blood glucose, fibrinogen, homocysteine, folates, von Willebrand Factor (vWF), serum creatinine (with a glomerular filtration rate estimation with the Modification of Diet in Renal Disease formula) were measured after an overnight fast using a standardized venous blood sampling technique. A 24-hour urine collection was performed to measure microalbuminuria.

Subclinical Cardiovascular Disease
Carotid intima media thickness: ultrasonography of both left and right common carotid arteries was performed using a high-resolution B-mode system with a 7.5-MHz linear array transducer (ATL Apogee 800+). The arterial wall segments were assessed in a longitudinal view, strictly perpendicular to the ultrasound beam, with both walls clearly visible to achieve diameter measurements. The actual IMT measurements were performed on the far wall along a
minimum 10-mm length of an arterial segment with a high-quality image automatic acquisition using IOTEC software (IODP). Adventitia-to-adventitia diameter and intraluminal diameter of the common carotid artery were also measured. In our laboratory, the intra- and interobserver reproducibilities were 3.6±4% and 6.8±4.5%, respectively. Plaque of common, internal, and external carotids was considered as a focal structure encroaching into arterial lumen of at least 0.5 mm or demonstrated a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface.34

Pulse wave velocity (PWV) was measured noninvasively in the carotid–femoral segment using the automatic device Compilor (Colson, Paris, France). The validation of this automatic method and its reproducibility have been published previously in a paper authored by one of the authors (A.B.).35 Augmentation Index was assessed using high-fidelity applanation tonometry (SphygmoCor Pulse Wave Analysis; PWV Medical Pty Ltd, Ermington, Sidney, Australia) as described previously.36

Measurements of flow-mediated and endothelium-independent vasodilatation (nitroglycerin-mediated dilatation) were assessed as described by Weidinger’s group.37 Plasma (citrated) vWF antigen concentrations were measured by immunoturbidimetry (STA-Liatest-vWF 00518; STAGO, Asnières, France).

Left ventricular hypertrophy was defined by the presence of Sokolow-Lyon (>38 mm) and/or Cornell product (>2.440 mm·ms) indices on electrocardiography.38

Statistical Analysis
The number of subjects enrolled in the study was enough to detect with a 5% 2-tailed significance level and an 80% power difference between means ≥0.4 SD.

Continuous variables were compared using the Mann-Whitney test and categorical ones using the χ² test or the Fisher test when needed. Candidate factors for multivariate logistic regression analyses of memory score (<0; primary end point) and WMH (Fazekas score >1, secondary end point) as dependent variables were first selected on a pathophysiological basis using a limited number of pathophysiological hypotheses; the models tested the influence of age, gender, diabetes, smoking, body mass index, total cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting glucose, Fazekas grade, and 18 parameters pertaining to 6 vascular phenotypes: 24-hour SBP and DBP or optimum BP control (ie, 24-hour SBP <130 and DBP <80 mm Hg), hypertension duration (BP), brachial artery diameter, carotid artery external and internal diameter, carotid artery wall cross-sectional area, IMT and blood folate levels (arterial structure), plaque presence (atherosclerosis), flow-mediated dilatation and vWF (endothelial function); PWV and Augmentation Index (AS), estimated glomerular filtration rate, microalbuminuria (<30 versus ≥30 mg/d), and left ventricular hypertrophy (other target organ damage). Further selection was performed on a statistical basis; the less significant factors were eliminated interactively and progressively until a final model could be reached. This procedure allowed us to lose the minimum number of observations due to missing data. The final models explained 9.5% (P=0.0002) and 24.6% (P=0.0005) of the total variance for the memory function score and WMH, respectively. No interaction was found between factors in the final models.

Adjusted relative levels in the Fazekas score subgroups were computed from multivariable analysis of variance estimates.

All analyses were performed using the SAS software R8.2 (SAS Institute, Cary, NC). The nominal significance level was set to P=0.05.

Results

Patient Characteristics
Patient characteristics are summarized in Figure 1 and Tables 1 and 2 with 76% patients recruited through the local press and 24% enrolled by the Clinical Investigation Centre general practitioner network. The average results for the group of the main cognitive tests were: Mini Mental State Examination 28.3±1.4, depression scale: 6.4±3.1, and Grober-Buschke test: free recall 35±18 and cued recall 87±16. All patients fulfilled 4 of 5 items of the Petersen criteria of MCI, and 69% met all 5 criteria, including a Grober-Buschke objective memory impairment score <44.9 There was no statistically significant difference between the subgroups fulfilling 4 or 5 MCI items, respectively, in all collected variables. Therefore, we conducted the multivariate analysis in the whole study population.

Men and women, despite similar ages, differed significantly in terms of memory score (men: −0.46±1.11; women: +0.24±1.02; P<0.0001) and visual capacity score (men: +0.13±0.98; women: −0.15±0.95; P=0.025). Of note, neither verbal fluency nor WMH severity differed significantly according to gender.
Arterial Variables Associated With Impaired Memory Function

A significant, independent, and positive association was observed only between the memory score and male gender (OR, 3.24; 95% CI, 1.78 to 5.94; \( P/H11005 0.0001 \)) with trends for an association with WMH (\( P/H11005 0.09 \)) and with PWV (\( P/H11005 0.09 \)). The strong influence of gender led us to perform different models for men and women. In male patients, PWV was the only significant predictor (OR, 1.22; 95% CI, 1.00 to 1.49; \( P/H11005 0.05 \)). No significant association of the tested parameters with the memory score was detected in women. Regarding verbal fluency or visual memory capacity scores, no significant association was observed.

Variables Associated With White Matter Hyperintensities

A significant association was observed between WMH presence and age (per 5 years 1.45 [1.02 to 2.06]; \( P=0.04 \)), IMT (per 0.1 mm: 1.58 [1.01 to 2.49]; \( P=0.05 \)), Augmentation Index (per 5%: 1.24 [1.01 to 1.53]; \( P=0.04 \)), and plasma vWF (per 20%: 1.28 [1.07 to 1.53]; \( P=0.006 \)), whereas a weak trend toward an association with increased 24-hour ABPM DBP (per 10 mm Hg: 1.49 [0.9 to 2.46]; \( P=0.12 \)) was observed. Moreover, age, IMT, plasma vWF, and Augmentation Index (but not DBP) after adjustment for the other variables were associated independently with the severity of WMH (Figure 2). Of note, no significant association with gender was observed.

Discussion

To the best of our knowledge, we report here the first study dedicated to an integrative biochemical risk factor and vascular assessment (including ABPM, arterial stiffness and thickness, atherosclerotic plaque, endothelial function, and WMH measurements) in elderly hypertensive patients with SMC, a population at risk to develop dementia. After adjustment for the usual cardiovascular risk factors, arterial stiffness in men, as assessed by PWV, was significantly and independently associated with memory impairment. More-
over, regardless of gender, the severity of WMH was independently associated with increased carotid IMT and stiffness (as assessed by augmentation index) as well as with increased age and plasma levels of vWF, a biomarker of endothelial damage.

It is expected that treating hypertension could be effective in preventing dementia because of the association of high BP with atherosclerosis as well as with WMH,\textsuperscript{39} cognitive decline, vascular dementia, and AD.\textsuperscript{40} However, inconsistent results from randomized, controlled trials have led to a controversy regarding whether antihypertensive treatment may prevent the development of cognitive dysfunction.\textsuperscript{41} In our study, elderly hypertensive patients selected on the basis of SMC displayed satisfactory BP control on average as assessed by APBM. Neither WMH severity nor memory score were correlated independently to ABPM or optimum BP control or hypertension duration. Moreover, even if mean SBP on ABPM was significantly associated with PWV and IMT in our study population (data not shown), other target organ damage (left ventricular hypertrophy, microalbuminuria, estimated glomerular filtration rate) were not associated with either WMH or memory score when included in our multivariate models. Our results indicate that among hypertension-induced target organ damage, vascular changes are more specifically associated with cognitive dysfunction and WMH.

Our results concerning the association between cognitive decline and increased AS extend the results of the very few reported data obtained so far. None of the previous studies investigated specifically elderly hypertensive patients and SMC. Mizushima et al reported that PWV was increased in 16 elderly patients presenting with VaD compared with 18 patients with AD and 44 control subjects.\textsuperscript{7} Nagai et al reported that PWV was correlated independently with cognitive function in 27 subjects presenting either with AD or MCI.\textsuperscript{8} Hanon et al\textsuperscript{9} led a cross-sectional study in 308 consecutive elderly subjects (mean age, 78 years; 64% women; 76% hypertensives) presenting to a memory clinic with normal cognitive function (26%), MCI (27%), AD (41%), or VaD (6%) and found that higher PWV was associated with poorer cognitive function. As compared with subjects with normal cognitive function, PWV was higher in patients with VaD or AD and intermediate in patients with MCI, suggesting that functional changes of the arterial system could play a role in the pathogenesis of both VaD and AD.\textsuperscript{9} Similarly, Scuteri et al investigated 146 elderly patients referred for memory deficit (mean age, 79 years; 71% women; 61% with hypertension) and reported that increased PWV was the single strongest predictor of subsequent cognitive decline after a median follow-up of 12 months.\textsuperscript{10} In contrast, in a population-based study in 400 men between 40 and 80 years of age, Muller et al reported that subjects with either subclinical (as defined by increased AS or thickness or lower ankle–brachial index) or prevalent cardiovascular disorders displayed a decreased memory performance. Increased IMT was related to decreased memory performance, and only a nonsignificant association was observed between increased PWV and decreased processing capacity and executive functioning.\textsuperscript{27} In the Rotterdam population-based study of 2767 elderly subjects aged $\geq 55$ years (mean age, 71 years; 58% women), Poels et al reported an association between AS and the Stroop test in cross-sectional analysis but did not find an association with cognitive decline or risk of dementia over time. The authors acknowledged, however, that they could not rule out completely an association with the risk of VaD because of the low number of incident vascular cases.\textsuperscript{4} In our present study, an association between AS and memory impairment was only observed in men suggesting possible differential effects in hypertensive patients of gender at an early stage of cognitive impairment. Hanon et al\textsuperscript{8} as well as Scuteri et al\textsuperscript{42} did not observe gender differences. However, both studies enrolled older patients with a wider range of cognitive patterns, not all of them with hypertension.
over, in our study, in accordance with previous data, men displayed greater memory impairment, and differed significantly from women in terms of cardiovascular risk factors, including increased AS. Of note, male gender was the strongest independent predictor of PWV in multivariate analysis (data not shown), which may contribute to the differential association of PWV with the cognitive decline regarding gender. Prospective studies are required to determine whether such a gender-specific pattern may influence the transition from SMC to dementia.

We also investigated WMH and report an association between memory score and WMH severity. This result is consistent with the findings of previous reports showing that the severity of WMH is associated with MCI and dementia. This association was only marginally statistically significant, probably because of a lack of power as compared with previously published large population-based studies. The pathophysiology of WMIL is still unclear. Associations of WML with several risk factors (including diabetes and hypertension) have been reported, and some authors have proposed the use of MRI as a potential surrogate marker of cerebral small vessel disease. Alteration of deep small vessels such as arteriolosclerosis is indeed considered to play a central role in the development of WML. Interestingly, a significant and independent association between retinal circulation parameters and carotid IMT, a surrogate marker of atherosclerosis, has been described recently in patients with coronary artery disease. In the present study, increased carotid IMT was associated independently with increased WML. This is consistent with the Cardiovascular Health Study data, which showed that increased carotid IMT was independently associated with increased WML. However, neither AS nor endothelial function was assessed in this study.

In our study population, WMH were also associated independently with high vWF plasma concentrations, a surrogate of endothelial dysfunction. This is in accordance with data obtained in a community-based setting showing that baseline intercellular adhesion molecule plasma concentrations, another biomarker of endothelial cell activation, are associated with WMH lesion progression. Hoth et al reported recently preliminary results in 25 nondemented older adults with cardiovascular disease suggesting that impaired endothelial function (endothelial-dependent but not endothelial-independent vasodilatation) is associated with WMH. In our study population, which displayed different clinical features, endothelial-dependent vasodilatation was not found to be associated significantly with WMH in multivariate analysis. In contrast, blood levels of vWF, potentially a better independent surrogate for endothelial function, may be more closely associated with brain lesions.

Our results may provide new insights in the pathogenesis of WMH, because they strongly point to the association of WMH with both increased carotid arterial thickness and stiffness, together with endothelial damage, independently of age and BP.

Our study has some limitations. The observational study design does not allow the ascertaining of causality. In addition, the cross-sectional design does not allow testing for temporal changes, eg, the quality of control of BP over time could not be assessed and we are aware that including a subgroup of nonhypertensive SMC would have helped to better establish the value of vascular measures above and beyond hypertension. It is unknown whether the observed vascular abnormalities may have preceded the occurrence of cognitive decline and WMH. In particular, we cannot rule out that increased plasma vWF concentrations may be a simple covariate to, or a consequence rather than a cause of, WMH. The MRI methods used in the present study, which represented the state of the art at the time the scans were performed, were semiquantitative; quantitative automated measurements may yield more robust associations. Assessments of middle cerebral artery velocity, pulsatility index, cerebrovascular resistance, and cerebrovascular conductance were not undertaken, which may have provided an estimate of how closely peripheral measurements reflect central changes. Finally, all our patients were taking antihypertensive medication (however, not correlated significantly either with the memory score or with WMH considered as continuous variables; data not shown) and some were taking other drugs with vascular effects. The influence of multiple treatments on the assessed parameters as well as on the observed associations cannot be evaluated reliably.

Strengths of the current study include concomitant comprehensive vascular assessment with ultrasound, MRI, and biomarkers performed by experienced physicians using standardized procedures and blind to the patient’s clinical features. Extensive vascular investigation included structural and function assessments of both large arteries, endothelium function, and indirectly brain small vessels. ABPM was used to control for BP.

Our data support strongly the hypothesis of a vascular influence in the setting of SMC in elderly hypertensive patients. To clarify whether the vascular abnormalities detected could predict further cognitive impairment, we are currently planning a longitudinal follow-up of the patients applying the same design of integrated vascular, MRI, and cognitive assessments. Establishing causal and temporal relation may help identify AS and thickness and endothelium function as therapeutic targets, beyond BP-lowering, for the prevention of cognitive decline and therefore of dementia.

Summary

Our results suggest that arterial thickness, stiffness, and endothelial function should be evaluated together in the setting of SMC in elderly hypertensive patients, because each of them is independently associated with the extent of WMH, whereas increased AS in men is associated additionally with memory decline.

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Disclosures

None.

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