Dementia represents one of the principal neurological disorders in the elderly. Aging is associated with a large increase in the prevalence and incidence of degenerative and vascular dementias (VaDs), leading to a devastating loss of autonomy. In view of the increasing longevity of populations worldwide, prevention of dementia has turned into a major public health challenge. Alzheimer disease (AD) and VaD are the most common subtypes of dementia. Recent studies have indicated that vascular risk factors are involved in the pathogenesis of cognitive disorders and dementia. VaD and AD have been associated with cerebrovascular diseases, hypertension, diabetes, hypercholesterolemia, and atherosclerosis. Recent data have emphasized the observation that a high pulse pressure is associated with an increased risk of AD. Because an increased pulse pressure is a clinical indicator of arterial stiffness, it could be postulated that functional changes of the arterial system are involved in the pathogenesis of dementia, as suggested by the recent paradigm of "vascular impairment." In this context, 2 preliminary studies have shown a positive correlation between arterial stiffness and cognitive impairment in small samples in subjects with nonvascular dementia or VaD. Moreover, a recent pilot study reported an association between pulse wave velocity (PWV) and cognitive impairment in 84 elderly subjects referred for memory deficit.

The objective of our study was to evaluate the correlation between arterial stiffness and cognitive function in a larger population of elderly subjects. We studied a group of elderly subjects with symptoms of memory impairment to increase the prevalence of dementia in our sample compared with the general population. Patients were categorized in 4 groups according to their cognitive status assessed by a thorough neuropsychological evaluation: normal cognitive function, mild cognitive impairment (MCI), AD, or VaD. The primary

Key Words: cognitive disorders ■ elderly ■ hypertension
outcome was to assess the relationship between PWV and cognitive status after adjustment for confounding factors. Furthermore, correlations between PWV and scores on cognitive tests were performed as secondary outcomes.

Methods

Study Population

The study group was part of a cohort of elderly ambulatory subjects with symptoms of memory loss attending a geriatric outpatient clinic. We selected 308 consecutive elderly subjects from this cohort of patients presenting to a memory clinic between January and June 2003. Patients were eligible for the study if they were >60 years of age, had a memory symptom, and lived at home. Patients with major depressive states, psychiatric deficits, metabolic disorders, or other types of dementia than AD and VaD (eg, Lewy body disease, frontotemporal dementia, Parkinsonian dementia, etc) were excluded. All subjects gave written informed consent for their participation in the study, which was approved by the local ethics committee.

Assessment of Cognitive Function

The global cognitive assessment of patients was based on the Mini Mental State Examination (MMSE)12 performed by the physician. A validated comprehensive battery of neuropsychological tests, the cognitive efficiency profile (CEP)13 was performed by trained psychologists. This battery assesses the main cognitive areas: immediate and delayed memory (free and cued recall), language, visuo-perceptual and visuospatial capacities, praxia, gnosia, executive function, attention, and judgment. The detailed presentation of this battery, which has been shown to detect early impairment of cognitive function, has been described previously.13 The global CEP score is out of 100 (the higher the score, the better the cognitive function). The incidence of cognitive loss on functioning in daily life was evaluated by caregiver interview using instrumental activities of daily living (ADL)14 and ADL15. The educational level was scored according to a 3-degree scale corresponding to primary, secondary, and higher education. A complete physical examination including computed tomography brain scan, thyroid hormone, and B12 and folate levels was also performed.

At the end of the evaluation, subjects were classified into 4 subgroups: those with AD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria,16 those with VaD according to NINDS-AIREN (Association Internationale pour la Recherche et l’Enseignement en Neurologie) criteria,17 those with MCI by Petersen criteria,18 and those with normal cognitive function. The normal group comprised subjects with no disease known to alter cognitive function. They had normal scores on the CEP according to age, gender, and education (score > mean – 1.5 SD)13 but with no impact on ADL. This concept of MCI is useful in clinical practice to classify the “in-between” population (ie, individuals who are cognitively impaired but not demented). The cut score of −1.5 SD below the mean was chosen to be consistent with published criteria for MCI.18

Demographic Data

Demographic data were recorded during the consultation. Blood pressure was measured twice, after ≥5 minutes of rest in sitting position using a validated digital electronic monitor (OMRON 705 CP) and the mean of the 2 measurements taken.

Arterial Stiffness

Arterial stiffness was evaluated by carotid-femoral PWV measurement using an automatic device (Complior; Colson) by one physician blind to the cognitive evaluation. This method, which allowed an online pulse wave recording and automatic calculation of PWV, has been analyzed extensively.19 Briefly, 2 pressure waves were recorded transcutaneously at the base of the neck for the right common carotid artery and over the right femoral artery. PWV was determined as the foot-to-foot velocity. Pulse transit time was determined as the average of 10 consecutive beats. The distance traveled by the pulse wave was measured over the body surface as the distance between the 2 recording sites. Aortic PWV was automatically calculated as the ratio of distance to transit time (PWV = D/t[m/s]). The validation of this automatic method and its reproducibility has been described previously with an intraobserver and interobserver repeatability coefficient of 0.935 and 0.890, respectively.19

Statistical Analysis

Results in the tables and text are expressed as mean±SD. A χ2 test was used for the group comparisons of qualitative variables, and an ANOVA was performed for quantitative variables. Single Pearson’s correlation coefficients were calculated to express the relationship between PWV and other covariates. A multivariate regression analysis was used to assess the relationship between PWV and MMSE or CEP scores, including variables that were correlated with PWV in the univariate analysis (age, gender, systolic blood pressure [SBP], antihypertensive therapy, and presence of cardiovascular diseases).

ANCOVA was used to compare PWV values between groups (normal, MCI, AD, and VaD), including age, gender, SBP, level of education, antihypertensive therapy, and presence of cardiovascular diseases as covariates. Multiple comparisons were performed using Bonferroni’s test to compare PWV in AD, VaD, and MCI groups with the normal group (without cognitive impairment).

Using a logistic regression model, we report the odds ratio (OR) and 95% CI of dementia (AD or VaD types) per 1 SD increment of PWV. The OR for dementia was calculated with the group of patients with normal cognitive function as referent. The 1 SD increment of the PWV of the group with normal cognitive function was chosen in the model (2 m/s). Age, gender, SBP, and education level were included in the logistic regression for adjustment. Statistical analysis was performed with the General Linear Models package from NCSS 6.0 software (Statistical Solutions Limited). A P value <0.05 was considered statistically significant.

Results

Characteristics of the Population

The characteristics of the population are summarized in the Table. There were 308 patients of whom mean age was 78±8 years, 64% were female, 26% had normal cognitive function, 27% had MCI, 41% experienced AD, and 6% experienced VaD. Both dementia types were at a moderate stage (mean MMSE score 19±6). Demented subjects (with AD or VaD) were older and had lower education level than nondemented patients. Subjects with VaD had higher SBP, and cardiovascular diseases were more prevalent than in those with AD or without dementia. Mean SBP/diastolic blood pressure (DBP) was 143±19/80±11 mm Hg; hypertension (history of hypertension or DBP(DBP ≥ 140/90 mm Hg) was observed in 76% (234 of 308) of patients; and 70% of hypertensive subjects (164 of 234) were being treated with antihypertensive therapy. Antihypertensive therapy included diuretics in 38% (62 of 164), angiotensin-converting enzyme inhibitors in 32% (53 of 164), calcium antagonists in 30% (49 of 164), β-blockers in 26% (42 of 164), angiotensin receptor blockers in 19% (31 of 164), and other antihypertensive drugs in 10% (16 of 164). Cardiovascular diseases were present in 25% of patients (78 of 308), including coronary heart disease in 11% (34 of 308), stroke in 4% (12 of 308), heart failure in 4% (12 of 308), or cardiac arrhythmia in 10% (31 of 308).
Relationships Between PWV and Cognitive Status
The Figure indicated the values of PWV according to the cognitive status of patients (normal cognitive function, MCI, AD, or VaD). The ANCOVA, including age, gender, SBP, education level, cardiovascular diseases, and antihypertensive therapy as covariates indicated a significant relationship between cognitive status and arterial stiffness ($P<0.0001$). The results showed a significant gradient in level of cognitive function in relation to PWV. PWV appeared significantly higher in subjects with VaD ($15.2 \pm 3.9$ m/s) or AD ($13.3 \pm 2.9$ m/s) than in those without cognitive impairment ($11.5 \pm 2.0$ m/s; $P<0.001$). Moreover, PWV was higher in subjects with MCI ($12.6 \pm 2.6$ m/s) than in those without cognitive impairment ($11.5 \pm 2.0$ m/s; $P=0.01$).

The ORs for dementia per 1 SD increment of PWV adjusted for age, gender, SBP, and education level were calculated using the group of patients with normal cognitive function as referent. For each 2 m/s increment in PWV, the adjusted OR was 1.73 (95% CI, 1.27 to 2.47; $P=0.001$) for AD and 3.52 (95% CI, 1.87 to 8.05; $P<0.0001$) for VaD.

Relationships Between PWV and Cognitive Performances on Neuropsychological Tests
A negative association was shown between PWV and cognitive function assessed on neuropsychological tests. Univariate analysis indicated that PWV was significantly inversely correlated with MMSE ($r=-0.27; P<0.0001$) and with CEP scores ($r=-0.32; P<0.0001$). Because PWV was also significantly associated with age ($r=0.28; P<0.0001$), SBP ($r=0.34; P<0.0001$), male gender ($r=0.15; P<0.01$), antihypertensive therapy ($r=0.14; P<0.01$), and the presence of cardiovascular disease ($r=0.13; P<0.05$), we performed a multivariate regression analysis adjusted for these confounding variables. After adjustment for age, gender, SBP, antihypertensive therapy, and presence of cardiovascular diseases, a significant relationship was observed between PWV and MMSE ($\beta=-0.091; SE=0.028; P<0.001$) and between PWV and CEP scores ($\beta=-0.029; SE=0.009; P<0.001$), indicating that subjects with higher PWV have worse cognitive function.

Discussion
The main finding of our study indicated a significant association between PWV and cognitive status in elderly subjects. Higher PWV was associated with poorer cognitive function. This relationship was independent of age, gender, SBP, antihypertensive therapy, and the presence of cardiovascular diseases. Arterial stiffness appeared to be an independent determinant not only of VaD but also of AD.

An increase in PWV reflects arterial stiffening as a result of structural and functional changes of the vascular tree. Our results support previous reports that have shown a relationship between dementia (VaD or AD types) and vascular disorders, suggesting that arteriosclerosis plays a role in cognitive impairment. In particular, several trials have demonstrated a deleterious effect of hypertension on cognitive function. In the Rotterdam Study, the presence of atherosclerotic plaques or wall thickening of the carotid artery were significantly associated with VaD and AD. Likewise, a
recent longitudinal study has shown\(^7\) that a higher pulse pressure is associated with increased risk of AD, suggesting that arterial stiffening could be involved in the pathogenesis of dementia. Several mechanisms may explain our finding of an association between increased PWV and cognitive impairment. Arterial stiffness may favor an increase in central pulse pressure, which may influence arterial remodeling at the site of the extracranial and intracranial arteries. Indeed, pulse pressure and arterial stiffness have been related to atherosclerosis or arteriosclerosis in large\(^23,24\) and small vessels.\(^25\)

Vascular mechanisms of cognitive impairment involve small-vessel diseases, which are associated with small infarcts (lacunae), white matter lesions, and cortical brain atrophy. Dementia may be the direct consequence of ischemic brain lesions, depending on the volume, location, and number of these vascular lesions.\(^26\) In addition, abnormalities of the white matter may be associated with cognitive impairment.\(^27\) An increased pulse pressure has been associated with the prevalence and severity of cerebral white matter lesions,\(^28\) and in a recent study, aortic stiffness appeared as an independent predictor of stroke in patients with essential hypertension.\(^29\) It has been suggested that the summation of cerebrovascular lesions, white matter changes, and pre-existent asymptomatic Alzheimer’s brain lesions may lead to dementia, even when each type of lesion, on its own, is not severe enough to induce dementia.\(^26\) Indeed, the presence of arteriosclerosis or lipohyalinosis of small vessels might be the origin of vascular cerebral lesions or chronic hypoperfusion of the white matter and thus contribute to the early expression of a subclinical AD, causing the threshold of dementia to be reached earlier.

AD is also associated with lesions in the cerebral microvessels (cerebral amyloid angiopathy, microvascular degeneration affecting the cerebral endothelium and smooth muscle cells, basal lamina alterations, luminal narrowing, hyalinosis, and fibrosis).\(^30\) All these vascular changes may compromise the function of the blood–brain barrier, leading to an increased vascular permeability and protein extravasation in brain parenchyma resulting in A \(\beta\)-amyloid accumulation and cognitive impairment.\(^31\) Furthermore, vascular endothelial cells could play a role in the secretion of the precursor substrate of the neurotoxic A \(\beta\)-protein, leading to the destruction of cortical neurons in AD.\(^32\) Likewise, endothelial lesions in AD have been related to the location and number of senile plaques,\(^33\) and it has been reported that \(\beta\)-amyloid could interact with vascular endothelial cells to produce an excess of free radicals.\(^34\) Recent reports have demonstrated that endothelial NO is also implicated in the regulation of PWV.\(^35\) Endothelial function appears impaired in the microcirculation as well as in large arteries of atherosclerotic animals and humans.\(^36\) These findings suggest that oxidative stress could be involved in the mechanisms of vascular disorders and AD.

One limitation of this work is the cross-sectional design of the study. Because the prevalence of dementia increases with age, the demented subjects were older than the nondemented. However, the association between PWV and dementia was observed after adjustment for age, gender, SBP, education level, antihypertensive therapy, and cardiovascular diseases, suggesting that the association between arterial stiffness and cognitive impairment is independent of these variables. To avoid several sources of error, we included a large sample of elderly subjects with symptoms of memory difficulties to increase the number of demented patients compared with the general population. Moreover, the assessment of cognitive function was performed in a memory clinic using highly specific and sensitive tests by trained specialists (physicians and neuropsychologists) to improve the quality of diagnosis of cognitive impairment. Subjects with a wide range of cognitive states (ie, normal cognitive function, MCI, and dementia [AD or VaD types]) were included to avoid selection bias in the assessment of the relationships between PWV and cognitive dysfunction.

In conclusion, our study indicates an independent correlation between arterial stiffness and cognitive impairment, supporting previous studies suggesting that functional changes of the arterial system could play a role in the pathogenesis of dementia (vascular or Alzheimer’s types). These results emphasize the necessity of longitudinal studies to determine whether arterial stiffness is indeed a risk factor for dementia.

Acknowledgments

This work was supported in part by a grant from the Association France Alzheimer. The authors gratefully acknowledge Professor Alexandra Bune (University of Sydney) for her assistance.

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Relationship Between Arterial Stiffness and Cognitive Function in Elderly Subjects With Complaints of Memory Loss
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Stroke. 2005;36:2193-2197; originally published online September 8, 2005;
doi: 10.1161/01.STR.0000181771.82518.1c

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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