

# Cerebrovascular Reactivity and Cognitive Decline in Patients With Alzheimer Disease

Mauro Silvestrini, MD; Patrizio Pasqualetti, PhD; Roberto Baruffaldi, MD; Marco Bartolini, MD; Yasmin Handouk, MD; Maria Matteis, PhD; Filomena Moffa, PhD; Leandro Provinciali, MD; Fabrizio Vernieri, MD

**Background and Purpose**—The aim of this study was to explore the possible contribution of alterations in cerebral hemodynamics to the evolution of cognitive impairment in patients with Alzheimer disease (AD).

**Method**—Fifty-three patients with AD were investigated. The evolution of cognitive decline over 12 months was evaluated by means of changes in Mini Mental State Examination (MMSE) and AD Assessment Scale for Cognition (ADAS-Cog) scores. Demographic characteristics, vascular risk profile, pharmacological treatment, and presence of white matter lesions were assessed at entry. Further, a basal evaluation of cerebrovascular reactivity to hypercapnia was measured with transcranial Doppler ultrasonography using the breath-holding index (BHI).

**Results**—Of all the variables considered, both MMSE and ADAS-Cog changes had the highest correlation with BHI, followed by age and diabetes. After subdividing both cognitive measures reductions into bigger and smaller-than-average decline (2 points for MMSE; 5 points for ADAS-Cog), multiple logistic regression indicated BHI as the sole significant predictor of cognitive decline.

**Conclusions**—These results show an association between impaired cerebral microvessels functionality and unfavorable evolution of cognitive function in patients with AD. Further research is needed to fully establish whether altered cerebral hemodynamics may be considered an independent factor in sustaining cognitive decline progression or an effect of pathological processes involved in AD. (*Stroke*. 2006;37:1010-1015.)

**Key Words:** dementia ■ hemodynamics ■ ultrasonography ■ ultrasonography, Doppler, transcranial

Vascular cognitive impairment and Alzheimer disease (AD) are considered the leading causes of irreversible cognitive decline.<sup>1</sup> Recently, the possibility of pathophysiological links between these 2 entities has been widely discussed and the strict distinction made between vascular dementia and AD criticized. The concept has emerged that in most conditions of dementia, degenerative and vascular lesions might not only coexist but also interact to exacerbate cognitive decline.<sup>2</sup> The apparently provocative statement that AD could be considered a vascular disorder<sup>3</sup> is actually based on suggestive observations. Epidemiological studies have evidenced that AD and vascular dementia share common risk factors.<sup>4</sup> Moreover, there is neuropathological evidence that vascular lesions and atherosclerotic occlusion of cerebral arteries may unmask or strengthen the clinical expression of AD.<sup>5,6</sup> An interesting hypothesis theoretically able to demonstrate a common pathogenetic basis for AD and cerebrovascular disease (CVD) proposes that accumulation of  $\beta$ -amyloid, which is held to be an important neurodegeneration mechanism, could simultaneously be the cause and the

consequence of cerebrovascular impairment, suggesting that pathogenetic factors of AD and CVD may produce not only additive, but actually synergistic, effects on the brain.<sup>7</sup> However, the hypothesis of a synergy between vascular and degenerative disorders has been criticized on the basis of neuropathological evidence suggesting a mere additive effect of cerebral infarctions on neurodegenerative lesion, the association of which would be casual.<sup>8</sup> From a practical point of view, the demonstration of a strict pathogenetic relationship between CVD and AD would have interesting implications, the most important of which relates to the possibility of extending CVD treatment options and preventive measures to the latter patients.<sup>9</sup>

In this study, we explored the possible contribution of alteration in cerebral hemodynamics to the progression of cognitive decline in a group of patients with mild or moderate AD.

## Methods

Patients were selected from consecutive subjects referred by general practitioners to the dementia outpatient service of the neuroscience

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From the Neurological Clinic (M.S., R.B., M.B., Y.H., L.P.), Polytechnic University of Marche, Ancona, Italy; Department of Neuroscience (P.P., F.M.), AfaR-Fatebenefratelli Hospital, Isola Tiberina, Roma, Italy; IRCCS Fondazione Santa Lucia (M.M.), Roma, Italy; and Neurological Clinic (F.V.), Campus Biomedico University, Roma, Italy.

Correspondence to Professor Mauro Silvestrini, Clinica Neurologica, Università Politecnica delle Marche, Via Conca 71, 60020 Ancona, Italy. E-mail masilvestrini@libero.it

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department of the Polytechnic University of Marche for progressive cognitive impairment from January 2002 to February 2004. Inclusion criteria were a diagnosis of probable AD according to National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association<sup>10</sup> criteria and a mild or moderate cognitive impairment defined as a score  $\leq 2$  of the Clinical Dementia Rating.<sup>11</sup> Patients with a clinical history of CVD, stepwise progression of cognitive impairment, presence of focal neurological signs, severe subcortical leukoencephalopathy, cortical infarction, hemodynamically significant neck and large intracranial arteries stenosis or occlusion, embolizing cardiopathy, medical conditions, and treatments interfering with the anatomic and functional properties of cerebral vessels were excluded.

Blood samples and clinical history were obtained from all subjects. The cardiological evaluation included ECG and transthoracic or transesophageal echocardiography. Selection of patients was performed by 2 neurologists with certified experience in managing patients with dementia after careful evaluation of clinical and instrumental exams.

Included patients underwent a structured clinical interview, a neurological examination, a neurosonological study of extracranial and intracranial vessels, and an extensive neuropsychological assessment of cognitive function including Mental Deterioration Battery, Trailmaking A and B, and Test of Judgment. The neuropsychological evaluation was repeated at the end of the follow-up period to confirm the diagnosis of AD.

Brain magnetic resonance images were obtained in all patients using a 1.5-T scanner with the spin-echo technique and T1-, T2-weighted, and fluid-attenuated inversion-recovery sequences to detect possible white matter lesions. These were graded according to Wahlund et al;<sup>12</sup> only patients without vascular lesions (grade 0) or with small subcortical focal lesions defined as high signal intensity areas on T2-weighted images, but isointense with normal brain parenchyma on T1-weighted images and classified as grade I were included.

Intracranial vessels were examined using transcranial Doppler (TCD) ultrasonography (Multidop X DWL; Elektronische Systeme GmbH). Cerebral vasomotor reactivity (CVR) to hypercapnia was evaluated by means of the breath-holding index (BHI), obtained by dividing the percent increase in mean flow velocity (MFV) occurring during breath-holding by the length of time (seconds) subjects hold their breath after a normal inspiration [(MFV at the end of breath-holding - rest MFV)/rest MFV  $\times 100$ /s of breath-holding].<sup>13</sup> A detailed description of the procedure for BHI evaluation has been described in detail previously.<sup>14</sup> Patients performed 3 evaluations. After each evaluation, the return to baseline values of flow velocity was documented. The BHI values included in the analysis were the means of the 3 tests and of right and left values.

Follow-up was performed 12 months after inclusion in the study. During this period, patients received acetylcholinesterase inhibitor donepezil (5 mg daily for 3 months and then 10 mg daily) in addition to the best therapy for each vascular risk factor. Compliance of therapy was checked periodically by means of telephone contacts and visits performed at 3-month intervals. Particular attention was paid to the control of vascular risk factors so to adapt therapy to obtain an optimal control of diabetes, hypertension, and hypercholesterolemia.

Progression of cognitive decline was investigated by means of the validated Italian versions of Mini Mental State Examination (MMSE) and AD Assessment Scale for Cognition (ADAS-Cog)<sup>15,16</sup> performed at entry and at the end of the follow-up period. Neuropsychological assessment was performed by a trained neuropsychologist who was blinded to the results of hemodynamics evaluations.

All included patients or caregivers gave written informed consent according to the Declaration of Helsinki. The study was approved by the local ethical committee.

Formal sample size calculation was not performed because this was an explorative study about the possible correlation between cerebral hemodynamics impairment and severity of cognitive decline progression. However, we considered as relevant a bivariate correlation of  $\geq 0.40$  (corresponding to 16% of accounted variance) and

calculated that a sample size of 50 patients would result in a power of 86% (with bilateral  $\alpha=0.050$ ).

Because the aim of the study was to seek whether and how severity of progression of cognitive decline could be related to cerebral hemodynamic impairment, this goal was best served by a regression model. A multiple regression analysis was applied to test the potential confounding role of demographic characteristics (sex, age, and education) and vascular risk factors (hypertension, diabetes, smoking habits, and hyperlipidemia), then the linearity of the relationship between cerebral hemodynamics impairment and severity of progression of the cognitive impairment was tested using a polynomial regression and the best-fitting model (maximum  $R^2$  and significant  $R^2$  change versus the previous model) was chosen.

To provide additional information potentially useful for clinicians, both outcome cognitive variables were dichotomized in 2 groups: above the median decrease (faster cognitive decline) and below (or equal to) the median decrease (slower cognitive decline). The risk of an above-average decline in relation to the hemodynamic impairment was evaluated using a logistic regression model. Odds ratios (ORs) and corresponding 95% CIs were calculated to quantify this effect.

## Results

A total of 168 patients with dementia were initially evaluated. In 87 patients, probable AD and mild to moderate cognitive impairment was diagnosed. Among them, 18 were excluded: 5 for cortical infarction or extensive white matter lesions, 4 for moderate to severe carotid stenosis or occlusion, 2 for respiratory or cardiac problems, and 7 for technical problems with TCD examination. Of the remaining 69 patients, 13 were lost to follow-up (3 patients died, and 10 refused to come for further evaluation), whereas in 3, the diagnosis of type of dementia was changed at the moment of the evaluation performed at the end of the follow-up period; in particular, in 2 patients emerged clinical elements suggestive of dementia with Lewy bodies and in 1 of vascular dementia.

The demographic and neuroradiological characteristics of the 53 patients who completed the study, risk factors, treatments, MFV, index of vasomotor reactivity (BHI) in the middle cerebral arteries, and scores of the MMSE and ADAS-Cog administered at baseline and at 1 year are reported in the Table. No patient reported stroke or transient ischemic attack during the follow-up period. There was considerable baseline variability of BHI values (coefficient of variation=37%; minimum=0.38; maximum=1.82), whereas MMSE scores (coefficient of variation=11%; minimum=14; maximum=22) and ADAS-Cog scores (coefficient of variation=14%; minimum=19; maximum=38) were more uniform, indicating that a fairly homogeneous sample in terms of cognitive impairment can be heterogeneous in terms of CVR.

Because the baseline cognitive status could be the first predictor of cognitive deterioration and should be taken into account,<sup>17</sup> MMSE and ADAS-Cog changes were adjusted with respect to the corresponding baseline measures (percentage of explained variance 16% for MMSE [ $P=0.003$ ] and 10% for ADAS-Cog [ $P=0.021$ ]). When adjusted MMSE changes were entered as dependent variable, the highest correlation was with BHI ( $r=0.519$ ;  $P=0.001$ ), followed by age ( $r=0.356$ ;  $P=0.004$ ) and diabetes ( $r=0.300$ ;  $P=0.015$ ). Because nearly all diabetic patients received antidiabetic drugs, this treatment was also associated with a greater decrease in MMSE scores ( $r=0.300$ ;  $P=0.036$ ). Neither

**Basal Characteristics, MMSE, and ADAS-Cog Scores (baseline and at 1 year) of the 53 Patients With AD**

Demographic data		
Age, years:mean, SD		70.3, 5.7
Gender, % of females		47%
Risk factors		
Hypertension, %		49%
Diabetes, %		19%
Hyperlipidemia, %		17%
Smoking, %		28%
Cardiopathy, %		9%
MRI findings		
Subcortical infarcts, %		24%
Drugs		
Statins, %		10%
Oral antidiabetics, %		16%
Antiplatelet agents		11%
Angiotensin-converting enzyme inhibitors, %		12%
Diuretics, %		14%
Ca-antagonists, %		10%
$\beta$ -blockers, %		4%
TCD data		
MFV, cm/s:mean, SD		49.72, 9.6
BHI, mean, SD		1.02, 0.38
Basal cognitive evaluation		
MMSE scores, mean, SD		17.5, 1.9
ADAS-Cog scores, mean, SD		30.0, 4.2
One-year cognitive evaluation		
MMSE scores, mean, SD		15.0, 3.0
ADAS-Cog scores, mean, SD		36.8, 6.9

small subcortical infarcts nor other variables were significantly related to progression of the cognitive impairment.

By applying the linear multiple regression model to the data, the decrease in MMSE scores can be described by the following formula:  $\text{MMSE change} = 1.34 - 0.79 \cdot \text{BHI}_{10} + 0.028 \cdot (\text{BHI}_{10})^2 + 0.08 \cdot \text{age}$  for  $0.38 \leq \text{BHI} \leq 1.82$ . This model accounted for 43% of MMSE decrease variance ( $P < 0.001$ ).

In Figure 1, top (where the age effect was taken into account but not represented for a simpler graphical presentation), this relationship is represented with corresponding 95% CI, suggesting that a steep decline in MMSE scores may be expected with a BHI  $< 1.0$ , whereas for greater values, the progression of cognitive impairment is weakly related with CVR. However, this model is not reliable for BHI values outside the range observed (ie, for patients with BHI  $\approx 2$ ); because among polynomial regressions, the quadratic ones resulted from the optimal model (maximizing the accounted variance with the minimum number of coefficients), a U-shaped curve would appear for  $x$  axis prolonged to higher BHI values. More subjects with high BHI values are needed to better explore the relationship outside the BHI range of the present study. As shown in Figure 1, bottom, when patients were subdivided into 4 BHI groups, although those with

higher BHI were not preserved against the cognitive decline (the 95% CIs do not include a 0 value, corresponding to lack of change), its extent was smaller than the one measured in the other BHI categories.

Similar findings were observed for ADAS-Cog changes. This was an expected result because a correlation of 0.831 was found between MMSE and ADAS-Cog. The regression model can be described by the following formula:  $\text{ADAS-Cog change} = 7.39 + 1.95 \cdot \text{BHI}_{10} + 0.064 \cdot (\text{BHI}_{10})^2 + 0.16 \cdot \text{age} + 2.68$  (if diabetes was present) for  $0.38 \leq \text{BHI} \leq 1.82$ .

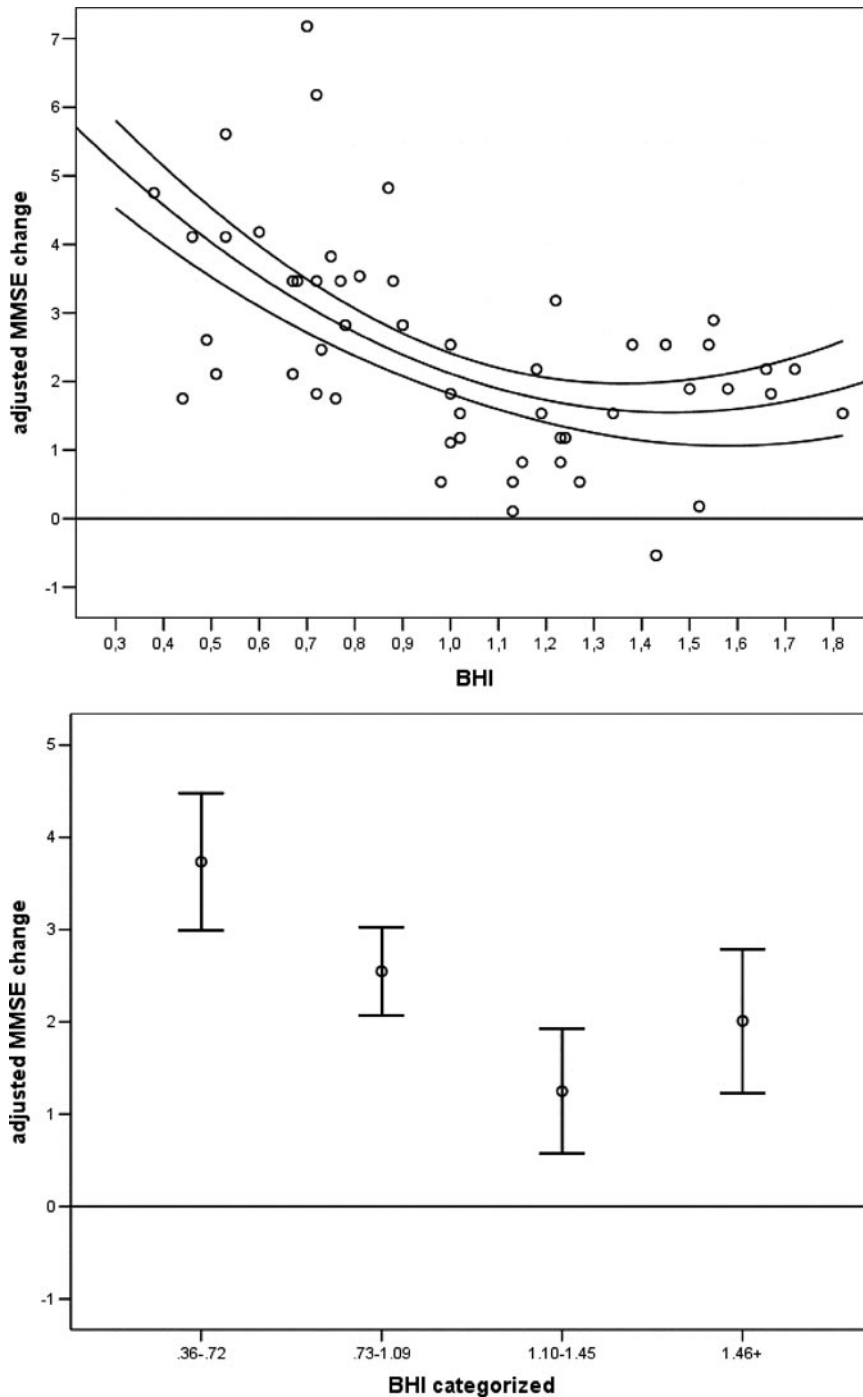
This model accounted for 56% ADAS-Cog increase variance ( $P < 0.001$ ). The only difference with respect to MMSE was that diabetes seemed to play a stronger role for ADAS-Cog changes. This effect and the overall higher percentage of explained variance could be ascribed to the higher sensitivity of ADAS-Cog.

The median reduction in MMSE scores was 2 points. When the reductions in MMSE scores were divided into those  $< 2$  or  $> 2$  points, the multiple logistic regression indicated that BHI was the only significant predictor of greater deterioration; more precisely, for each additional 0.1 BHI point, the odd of MMSE worsening was  $\approx 60\%$  lower (OR, 0.413; 95% CI, 0.259 to 0.658;  $P < 0.001$ ). Again, overlapping findings were found when dichotomized ADAS-Cog change (in this case, the median resulted equal to 5-point increase) was entered as dependent variable in the logistic model; for each additional 0.1 BHI point, the odd of ADAS-Cog worsening was  $\approx 57\%$  lower (OR, 0.434; 95% CI, 0.282 to 0.667;  $P < 0.001$ ). The estimated relationship between BHI and predicted probability of MMSE and ADAS-Cog worsening is represented in Figure 2. These consistent findings were attributable to the high agreement between the 2 dichotomized measures (Cohen's  $\kappa = 0.89$ ;  $P < 0.001$ ), with only 3 cases (6%) classified as fast worsening at ADAS-Cog and slow worsening at MMSE.

## Discussion

The possibility that vascular and degenerative processes may interact in compounding the cognitive decline experienced by AD patients is a controversial issue.<sup>18</sup> The hypotheses suggesting an additive or a synergistic effect between cerebrovascular impairment and neurodegeneration are the most interesting. It is still unclear whether CVD is directly related to the pathogenesis of AD. Studies supporting this view have shown that the reduction in cerebral blood flow is greater in AD patients than in healthy controls.<sup>19</sup> In addition, vascular risk factors have been seen to be associated with cerebral atrophy,<sup>20</sup> and it has been suggested that brain atrophy can result from an ischemic process.<sup>21</sup>

Our results, showing an association between reduction of CVR and greater extent of cognitive decline at 12 months, refer to a highly selected population of AD patients. This was in part because of the severity of inclusion–exclusion criteria. Moreover, technical problems that made impracticable CVR assessment in some cases and the refusal to perform follow-up evaluation by some patients reduced the number of subjects initially involved in the study. Despite this limit, our data further suggest a contribution of vascular factors to the pathogenesis of cognitive impairment in some patients with AD. This is in line with the previous observation that



**Figure 1.** Top, Relationship between BHI and deterioration in MMSE scores according to a polynomial regression model that accounted for 43% of variance. Bottom, Mean values (and 95% CI) of MMSE deterioration in patients subdivided into 4 BHI intervals. Also, patients in the groups with high cerebrovascular reactivity exhibited cognitive decline, although the decline was about one third with respect to the group with the poorest cerebrovascular reactivity.

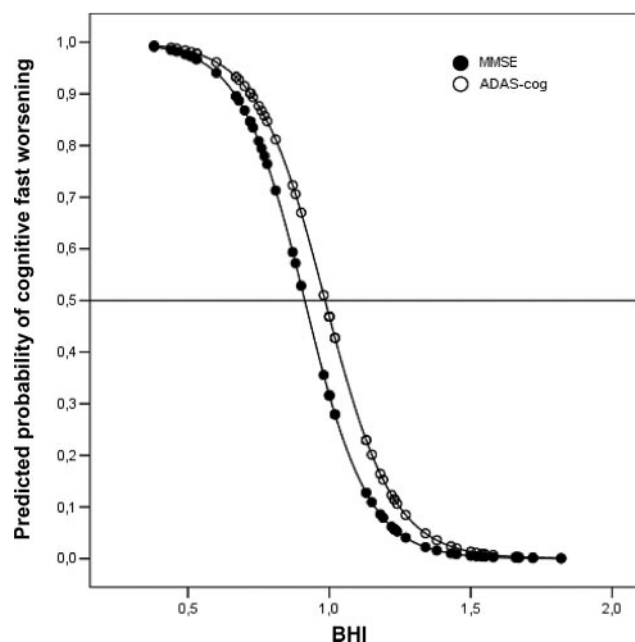
impaired cerebral blood flow in AD may be related to an engagement of microvessels as a possible consequence of various pathological processes like cerebral amyloid angiopathy, arteriolosclerosis, capillary endothelial, and basement membrane changes.<sup>22</sup> Alteration of CVR in the absence of neck vessels severe stenosis may reflect increased arteriolar wall stiffness attributable to intrinsic anatomical changes.<sup>23</sup>

In the present study, diabetes and antidiabetic therapy were the only risk factors associated with MMSE worsening. There is evidence that diabetic patients have an impaired vasodilatory response to hypercapnia, at least partially ascribable to autonomic dysfunction.<sup>24</sup> Small subcortical infarcts in 24%

of our patients did not correlate with prognosis or with altered cerebral hemodynamics. Although this may appear surprising given that changes of CVR seem to be common in patients with white matter vascular lesions,<sup>25</sup> all our patients had minimal focal vascular subcortical lesions on magnetic resonance.

For the evaluation of CVR, we used the breath-holding method, which has the advantages over more common approaches, such as acetazolamide injection and carbon dioxide inhalation, of better tolerability and rapidity of performance. On the other hand, the major problem is related to the necessity to obtain a full collaboration by the patients.





**Figure 2.** Probability of fast cognitive decline as measured with MMSE (●) and ADAS-cog (○) as a function of BHI values as predicted by the logistic regression model. The probability of a fast MMSE decline exceeds the probability of a slow decline when BHI was  $<0.91$ . When ADAS-Cog was considered, the critical BHI point was slightly higher (0.98).

This last aspect did not allow a second evaluation of CVR at the end of the follow-up period, when some patients were no more able to correctly perform apnea because of an advanced cognitive deterioration. The demonstration of a faster progression in CVR alteration in patients with a greater decline of cognitive scores would have suggested the possibility that cerebral hemodynamics failure can be considered a consequence of AD pathology. Even for this reason, the present study does not allow a conclusive interpretation about the pathophysiological correlation between vascular factors and cognitive decline in AD patients. Our findings can be interpreted as evidence of an additive or concomitant effect of vascular and degenerative mechanisms in the pathogenesis of AD or, alternatively, suggest a pathogenic involvement of vascular factors in determining cognitive decline.

In the present study, the evaluation of cognitive decline progression was based on MMSE and ADAS-Cog changes. Even if the use of other scales would have probably added some important information about changes in cognitive abilities, we are quite confident about the reliability of our approach. In fact, MMSE and ADAS-Cog are considered reliable for detecting cognitive changes in AD patients submitted to different therapeutic approaches. Moreover, the very high correlation between MMSE and ADAS-Cog scores further strengthens our findings and significantly reduces the possibility of mistake in recognizing subjects with different extent of cognitive decline progression.

Apart from these questions, the most interesting aspect to come out of our study relates to the possibility of obtaining by means of a simple evaluation of cerebral microvessel function useful information for the identification of AD patients who are at significant risk of a rapid and pronounced evolution of

cognitive impairment. The possibility of influencing cerebral microvessel function through a more aggressive therapeutic control of vascular risk factors could have favorable practical implications for the management of AD. This also seems to be suggested by observations showing a role for vascular risk factors in influencing not only the probability of developing vascular cognitive impairment but also AD.<sup>1</sup> It is also worth highlighting that the positive effects on cognitive decline evolution exerted by some pharmacological approaches could be influenced by their effects on cerebral vessel function as well as by a conventional action on vascular risk factor modulation. This applies to angiotensin-converting enzyme inhibitors<sup>26</sup> and statins,<sup>27</sup> which showed an effect in reducing the risk of dementia and the progression of cognitive impairment. Both classes of drugs affect the modulation of the vasodilation properties of cerebral vessels and are able to induce a significant improvement of cerebral hemodynamics.<sup>28,29</sup> The latter aspect deserves further attention in terms of the scope for developing novel therapeutic strategies, at least in a subgroup of AD patients with impaired cerebral hemodynamics.

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