Cognitive Deterioration in Bilateral Asymptomatic Severe Carotid Stenosis

Laura Buratti, MD; Clotilde Balucani, MD; Giovanna Viticchi, MD; Lorenzo Falsetti, MD; Claudia Altamura, MD; Emma Avitabile, MD; Leandro Provinciali, MD; Fabrizio Vernieri, MD; Mauro Silvestrini, MD

Background and Purpose—This study aimed to monitor cognitive performance during a 3-year period in subjects with bilateral asymptomatic severe internal carotid artery stenosis and to explore the role of cerebral hemodynamics and atherosclerotic disease in the development of cognitive dysfunction.

Methods—One hundred fifty-nine subjects with bilateral asymptomatic severe internal carotid artery stenosis were included and prospectively evaluated for a 3-year period. At entry, demographics, vascular risk profile, and pharmacological treatments were defined. Cognitive status was evaluated using the Mini-Mental State Examination at baseline and at follow-up. Cerebral hemodynamics was assessed by transcranial Doppler–based breath-holding index test. As a measure of the extent of systemic atherosclerotic disease, common carotid artery intima-media thickness was measured. A cutoff for pathological values was set at 0.69 for breath-holding index and 1.0 mm for intima-media thickness.

Results—The risk of decreasing in Mini-Mental State Examination score increased progressively from patients with bilaterally normal to those with unilaterally abnormal breath-holding index, reaching the highest probability in patients with bilaterally abnormal breath-holding index (P<0.0001). Pathological values of intima-media thickness did not influence the risk of Mini-Mental State Examination score change.

Conclusions—Our findings suggest that patients with asymptomatic bilateral severe internal carotid artery stenosis may be at risk of developing cognitive impairment. The evaluation of the hemodynamic status, besides providing insights about the possible mechanism behind the cognitive dysfunction present in carotid atherosclerotic disease, may be of help for the individuation of subjects deserving earlier and more aggressive treatments. (Stroke. 2014;45:2072-2077.)

Key Words: carotid stenosis ■ mild cognitive impairment ■ ultrasonography

The management of patients with bilateral asymptomatic carotid artery stenosis is still controversial. No clear evidence exists about the most effective treatment strategies to change patients’ prognosis, including timing and sequence of revascularization.1 We recently reported that asymptomatic subjects with severe narrowing of internal carotid artery (ICA) lumen may present a reduction in cognitive performances attributable to the activity of the hemisphere ipsilateral to the stenosis,2 and in some cases, it may develop a cognitive deterioration.3 Such consequences are more common if cerebral hemodynamics in the territory supplied by the stenotic ICA is altered.3 Furthermore, patients with bilateral carotid stenosis may present a reduction in specific cognitive domains depending on the more hemodynamically compromised brain hemisphere.4 To date, there are no available data on the long-term cognitive monitoring in these subjects. This study aimed at monitoring cognitive performances for a 3-year period in subjects with bilateral ICA stenosis and no previous sign or symptoms of ischemic cerebrovascular disease. To explore the possible mechanisms responsible for cognitive dysfunction, we also evaluated cerebrovascular reactivity (CVR) as a measure of the brain hemodynamic status and the common carotid artery wall thickness as a measure of systemic atherosclerotic disease.

Methods

This prospective study was performed at the Vascular Ultrasound Laboratory of the Neurological Clinic, Marche Polytechnic University Hospital (Ancona, Italy) from January 2003 to August 2010 among subjects referred by their primary care physicians because of their symptoms of ischemic cerebrovascular disease. To explore the possible mechanisms responsible for cognitive dysfunction, we also evaluated cerebrovascular reactivity (CVR) as a measure of the brain hemodynamic status and the common carotid artery wall thickness as a measure of systemic atherosclerotic disease.

Neck and intracranial arteries were evaluated using a color-coded duplex sonography (iU22 Philips Ultrasound, Bothell, WA). Quantification of stenosis was made on the basis of the presence of plaque at the grayscale and color Doppler imaging and on velocity criteria: ICA peak systolic velocity, end-diastolic velocity, and ICA/common carotid artery peak systolic velocity ratio.5 Patients with
ultrasound evidence of stenosis ≥70% in both ICAs without history of stroke and transitory ischemic attack were considered for enrollment. The asymptomatic status was determined through a detailed patient’s history review and a complete neurological examination to exclude any neurological signs.

Baseline global cognitive function was evaluated using the Mini-Mental State Examination (MMSE)\(^6\) adjusted for age and education. To minimize the effect of potential confounders, we adopted the following exclusion criteria: age ≥85 years, carotid occlusion or vertebrobasilar, and intracranial steno-occlusive lesions evaluated according to validated criteria,\(^7\) referred or documented cardiac failure (defined as a left ventricular ejection fraction <50%), referred or documented or treated cognitive impairment from any cause or any severe psychiatric disease, previous disability, including significant visual and hearing impairment, defined by the modified Rankin Scale >3, preexisting cerebrovascular disease, or coexisting severe medical conditions, interfering with the possibility to perform a follow-up. Furthermore, we excluded subjects with poor temporal acoustic window or not compliant to CVR testing.

Hypertension, diabetes mellitus, and hyperlipidemia, defined according to international guidelines,\(^4, 10\) were recorded when referred by the patient and documented in patients’ medical records or under current medical treatment; subjects were defined as smokers if smoking regularly ≥1 cigarettes per day; we recorded, referred, or documented the history of myocardial infarction (MI) or coronary heart disease (CAD) and peripheral arterial disease and referred, documented, or treated atrial fibrillation (AF); heavy drinking was defined as more than clearly moderate drinking (ie, estimated intake of ≥200 g of pure alcohol/wk constantly as disclosed by the patient or a relative). Pharmacological treatment of vascular risk factors was planned according to international guidelines.\(^11\)

The cerebral hemodynamic status was evaluated by testing the CVR (ie, a measure of the perfusion reserve reflecting the capability of cerebral arterioles to dilate in response to a vasomotor stimulus).\(^12\) CVR to hypercapnia was quantified by the transcranial Doppler–based breath-holding index (BHI) test,\(^12\) which consists of a voluntary apnea period. Bilateral transtemporal transcranial Doppler monitoring at the depth of proximal middle cerebral artery, 50±3 mm or M1 tract, was performed by an experienced sonographer blinded to the clinical status of the examined subjects. A head-frame was used to secure a stable angle of insonation.\(^11\) Mean cerebral flow velocities (MFVs) were recorded at baseline and at the end of BH. The exact length of apnea, measured by a capnometer (Oxy-cap, Datex, Italy), ranged from 29.6 to 30.3 s. The BHI is obtained by dividing the percentage increase in MFV occurring during BH by the length of time (s) subjects hold their breath after a normal inspiration ([MFV at the end of BH–baseline MFV]/baseline MFV×100 per s of BH).\(^12\) CVR was evaluated in the early morning. All participants performed 3 evaluations per side. Internal consistency of BHI measurements, treated as continuous variables, was tested with Cronbach\(^\alpha\) coefficient (left, \(\alpha=0.99\); variance range, ±0.022 and right, \(\alpha=0.99\); variance range, ±0.026), indicating a high reliability of BHI measurement among the 3 different readings. Similarly, if analyzed as a dichotomous value (normal versus pathological value), we observed a high Cohen \(\kappa\) index on both sides (left, \(\kappa=0.98\); right, \(\kappa=0.99\); \(P<0.05\), result obtained by comparing the 3 readings per each side). Using a binary approach, we did not observe discrepancies among observations; all BHI values resulting pathological at the first measurement were pathological also in the second and in the third one. The mean BHI value of the 3 tests was included in the analysis. On the basis of our previous results, we classified cerebral hemodynamic parameters as either impaired (BHI<0.69) or normal (BHI≥0.69).\(^12\) On the basis of BHI values, we classified subjects into bilaterally preserved CVR; bilaterally impaired CVR; and right CVR impaired and left CVR impaired.

Measurements of intima-media thickness (IMT) were performed at baseline according with international guidelines.\(^4\) To measure IMT, a semiautomatic software (QLAB version 8; Philips Medical Systems, Andover, MA) was used to improve measurement reliability and reproducibility.\(^4\) Carotid IMT was defined as the mean of both left and right side measurements. A cutoff for pathological values was set at 1.0 mm.\(^13\) All neck vessels ultrasound examinations were performed by the same 2 experienced operators. Inter-reader reliability was assessed by having the 2 sonographers blindly selected and redigitized a B-mode image from the 20-s videotape recording of a randomly selected set of 200 studies originally read by a third sonographer. One sonographer reread 130 studies for an inter-reader correlation coefficient of 0.88, and the second sonographer reread 70 studies for an inter-reader correlation coefficient of 0.85. Intra-reader variability was also assessed by having the 2 sonographers reread 70 randomly selected studies and resulted 0.92 and 0.91, respectively.

Patients were followed up for 3 years. Every 6 months, a clinical examination was performed. At the end of the follow-up period, all patients were reassessed with MMSE.

The study was approved by the ethics committee of the Marche Polytechnic University. All participants and caregivers gave their informed written consent according to the Declaration of Helsinki.

### Statistical Analysis

The main outcome measure was defined as the difference between MMSE at 3-year follow-up (f-MMSE) and MMSE at baseline (b-MMSE). Patients were categorized according to their BHI and IMT values. BHI values were combined into a single ordinal value: 0 (bilaterally normal values), 1 (right pathological), 2 (left pathological), and 3 (bilaterally pathological BHI). IMT values were treated as a dichotomous variable (normal and pathological). Age, b-MMSE and f-MMSE, and years of education were synthesized as continuous variables. Smoking habit, diabetes mellitus, dyslipidemia, hypertension, AF, peripheral arterial disease, and previous MI/CAD were collected as binary variables. The use of oral anticoagulants, statins, antidiabetics, antiplatelets, and antihypertensives was coded in 5 different dichotomous variables. Continuous variables were compared using the \(t\) test for independent samples. Binary variables were compared using the \(\chi^2\) test.

The relationship between f-MMSE and the predictors was analyzed first with 2 linear regression models, treating f-MMSE as a dependent variable and the continuous BHI values (left and right) as independent predictors.

Before other analyses, we performed an age- and sex-adjusted variance components analysis (a nested general linear model univariate analysis), to include in the final model; only the covariates significantly associated with a variance change in the estimated mean of the outcome. This evaluation included difference between b-MMSE and f-MMSE scores as outcome; the ordinal BHI and the binary IMT variables as predictors; age and sex as adjustments; and smoking attitude, diabetes mellitus, dyslipidemia, hypertension, AF, peripheral arterial disease, and MI/CAD as the covariates to be tested. Drugs were not included in both models because of high collinearity of these variables with the included comorbidities. We used an ANOVA (type III, sum of squares) method because this analysis reflected the same analytic process used in the final model.

To evaluate the effect of BHI and IMT on mean MMSE variance (from b-MMSE to f-MMSE), we set up different ANCOVA models for repeated measures. The main outcome was the paired b-MMSE and f-MMSE scores for each patient. All the models were adjusted for age, sex, hypertension, and AMI/CAD. The first model included left BHI value and right BHI value treated as continuous variables and analyzed in a full-factorial design. The second model was similar to the first one but included only the ordinal BHI value as a predictor. The third model considered left IMT value and right IMT value and treated as continuous variables in a full-factorial design. The fourth model analyzed both left and right IMT as binary in a full-factorial design.

The first final model consisted of a generalized multivariable linear model, adopting difference between b-MMSE and f-MMSE scores as outcome, using BHI as predictor, and age, sex, b-MMSE, hypertension, MI/CAD as covariates. To define the effect of IMT in each BHI class better, a second generalized multivariable linear model was set up using the intersection of BHI and IMT variables as predictor, adopting the same covariates. Statistical analysis was performed with SPSS 13.0 for Windows systems. Power analysis was performed with G*Power 3.1.7 for Windows systems.
Results
From a total of 206 subjects with bilateral asymptomatic carotid stenosis screened, 23 were excluded (5 were affected by dementia at the baseline, 4 for preexisting cerebrovascular disease, 2 because of coexisting severe medical conditions, 3 for poor temporal windows, and 9 that underwent carotid revascularization). Ninety-six of the 183 included subjects had been already enrolled in our previous study, exploring the relationship between cognitive performances and cerebral hemodynamic status. During the follow-up period, 7 patients had a vascular event (5 strokes and 2 MI), and 17 were lost at follow-up (8 died and 9 declined to attend the second cognitive evaluation). The final analysis was then performed on 159 subjects who completed the follow-up. A post hoc analysis showed that this number allowed to achieve a power of 0.93, with a t set to 0.05, in detecting small differences in the outcome ($F$ set to 0.0625).

Characteristics of subjects are reported in Table 1. No difference was detected between the 2 groups classified according to a normal or pathological IMT. According to the classification into different BHI groups, a difference was detected for dyslipidemia and MI prevalence. Furthermore, mean b-MMSE and f-MMSE values were significantly different among BHI groups. Values of b-MMSE were unrelated to basal hemodynamic compromise.

Both regressions resulted in statistically significant correlations, enlightening a close linear relationship between left or right BHI and the MMSE at follow-up (left side BHI, $r^2=0.838; P<0.0001$ and right side BHI, $r^2=0.828; P<0.0001$). Variance analysis showed that hypertension and a previous MI were the only 2 variables significantly associated with the variance of the outcome. Thus, we included these 2 factors in the final model, discarding the other factors. The first ANCOVA enlightened that left BHI ($P<0.0001$; partial $\eta^2=0.786$), right BHI ($P=0.019$; partial $\eta^2=0.593$), and the intersection of the 2 scales ($P=0.023$; partial $\eta^2=0.460$) contributed significantly to the model. The large partial $\eta^2$ values for left BHI, right BHI, and their intersection showed that they explained variations in MMSE. The second ANCOVA confirmed that also the ordinal BHI variable contributed significantly to MMSE variability ($P=0.001$; partial $\eta^2=0.108$). The MMSE mean difference from baseline to the end of follow-up was estimated at 1.830 points (95% confidence interval, 1.599 to 2.061; $P=0.0001$) with this model. The third ANCOVA showed that left IMT ($P=0.553$; partial $\eta^2=0.235$), right IMT ($P=0.764$; partial $\eta^2=0.156$), and the intersection of the 2 scales ($P=0.710$; partial $\eta^2=0.375$) did not contribute significantly to MMSE variability. We found similar results in the fourth model (data not shown). For this reason, we chose not to add IMT in the first final model.

Both multivariate models resulted in significant changes in predicting the outcome (Table 2; Figure). In the first model, a bilaterally pathological BHI resulted in significant association with higher MMSE scores difference at 3 years when compared with unilateral right ($P=0.0004$) or left abnormal BHI ($P=0.0001$) or bilaterally normal BHI ($P=0.0001$). The ordinal BHI variable contributed significantly to the variance of the outcome ($P<0.0001$; partial $\eta^2=0.208$). Both groups with unilateral impaired BHI showed a significantly higher difference in MMSE score when compared with patients with bilaterally normal BHI (right abnormal BHI versus bilaterally normal BHI, $P=0.005$; left pathological BHI versus bilaterally normal BHI, $P=0.032$). The intersection of the ordinal BHI variable and the dichotomous IMT value, analyzed in the second model, was significantly associated with the variance of MMSE difference ($P<0.0001$; partial $\eta^2=0.299$). However, this model confirmed the observations of the first one: MMSE score difference increased significantly from patients with bilaterally normal BHI to patients with unilaterally impaired BHI to those with bilaterally impaired values. IMT was not significantly associated with MMSE score variations even in the single subgroup, and it did not add any significant information.

**Table 1. Demographic and Clinical Characteristics of the Sample**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bilaterally Normal (n=56)</th>
<th>Right Pathological (n=32)</th>
<th>Left Pathological (n=27)</th>
<th>Bilaterally Pathological (n=44)</th>
<th>P Value</th>
<th>Normal (n=68)</th>
<th>Pathological (n=91)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>33 (58.9%)</td>
<td>23 (71.9%)</td>
<td>17 (63.0%)</td>
<td>25 (56.8%)</td>
<td>0.563</td>
<td>41 (60.3%)</td>
<td>57 (62.6%)</td>
<td>0.869</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>7 (12.5%)</td>
<td>7 (21.9%)</td>
<td>6 (22.2%)</td>
<td>10 (22.7%)</td>
<td>0.513</td>
<td>13 (19.1%)</td>
<td>17 (18.7%)</td>
<td>0.869</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>3 (5.4%)</td>
<td>3 (9.4%)</td>
<td>4 (14.8%)</td>
<td>5 (11.4%)</td>
<td>0.533</td>
<td>10 (14.7%)</td>
<td>5 (5.5%)</td>
<td>0.059</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>16 (28.6%)</td>
<td>18 (56.3%)</td>
<td>9 (33.3%)</td>
<td>13 (29.5%)</td>
<td>0.047</td>
<td>28 (41.2%)</td>
<td>28 (30.8%)</td>
<td>0.184</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>28 (50.0%)</td>
<td>22 (68.8%)</td>
<td>12 (44.4%)</td>
<td>27 (61.4%)</td>
<td>0.179</td>
<td>40 (58.8%)</td>
<td>49 (53.8%)</td>
<td>0.628</td>
</tr>
<tr>
<td>AF (%)</td>
<td>2 (3.6%)</td>
<td>3 (9.4%)</td>
<td>1 (3.7%)</td>
<td>1 (2.7%)</td>
<td>0.479</td>
<td>5 (7.4%)</td>
<td>2 (2.2%)</td>
<td>0.138</td>
</tr>
<tr>
<td>MI (%)</td>
<td>5 (8.9%)</td>
<td>9 (28.1%)</td>
<td>0 (0%)</td>
<td>7 (15.9%)</td>
<td>0.009</td>
<td>9 (13.2%)</td>
<td>12 (13.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>PAD (%)</td>
<td>3 (5.4%)</td>
<td>2 (6.3%)</td>
<td>5 (18.5%)</td>
<td>6 (13.6%)</td>
<td>0.200</td>
<td>8 (11.8%)</td>
<td>8 (8.8%)</td>
<td>0.600</td>
</tr>
<tr>
<td>Age (±SD)</td>
<td>69.80 (±3.60)</td>
<td>69.26 (±3.31)</td>
<td>71.30 (±4.36)</td>
<td>69.90 (±3.78)</td>
<td>0.185</td>
<td>69.73 (±3.63)</td>
<td>70.19 (±3.85)</td>
<td>0.444</td>
</tr>
<tr>
<td>Education (±SD)</td>
<td>10.64 (±4.66)</td>
<td>10.43 (±3.39)</td>
<td>10.59 (±3.52)</td>
<td>9.75 (±3.97)</td>
<td>0.715</td>
<td>10.39 (±3.61)</td>
<td>10.31 (±4.34)</td>
<td>0.891</td>
</tr>
<tr>
<td>b-MMSE (±SD)</td>
<td>27.03 (±1.35)</td>
<td>26.56 (±1.01)</td>
<td>26.55 (±0.80)</td>
<td>27.18 (±1.16)</td>
<td>0.040</td>
<td>26.75 (±1.05)</td>
<td>27.01 (±1.25)</td>
<td>0.167</td>
</tr>
<tr>
<td>f-MMSE (±SD)</td>
<td>26.12 (±1.46)</td>
<td>24.81 (±1.73)</td>
<td>25.00 (±1.27)</td>
<td>24.06 (±2.08)</td>
<td>0.000</td>
<td>24.86 (±1.85)</td>
<td>25.27 (±1.86)</td>
<td>0.174</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; b-MMSE, baseline Mini-Mental State Examination score; BHI, breath-holding index; f-MMSE, Mini-Mental State Examination score at the end of the 3-year follow-up period; IMT, intima-media thickness; MI, previous myocardial infarction; and PAD, peripheral artery disease.
to the predictive value of BHI on MMSE changes (Figure). In this second model, mean MMSE score difference estimates ranged from 3.191 (95% confidence interval, 2.605 to 3.778) in patients with bilaterally impaired BHI and pathological IMT to 0.503 (95% confidence interval, –0.247 to 1.253) in the group with bilaterally normal BHI and normal IMT.

**Discussion**

Our findings show that in patients with bilateral ICA stenosis, the probability of cognitive deterioration during a 3-year period is significantly associated with impairment in CVR. In fact, we found that the risk of a reduction in MMSE score after a 3-year period increased progressively from patients with bilaterally normal BHI values to those with unilateral abnormal BHI, reaching the highest risk in patients with bilateral BHI impairment. Counterintuitively, in our study, basal MMSE mean scores were within normal values in patients with preserved or altered CVR. A possible explanation for this finding is that according to the study protocol, subjects with referred, documented, or treated cognitive impairment from any cause were excluded a priori. The subsequent reduction in MMSE score observed in a subgroup of subjects of our cohort could represent the result of a chronic cerebral hypoperfusion occurring during the 3-year follow-up period.

A persistent increase in vascular resistance as a consequence of a steno-occlusive artery disease can be compensated by means of vasodilatation at the arteriolo-capillary level. This already existing intracranial vasodilatation can interfere with the ability of the cerebral vessels to dilate in response to demand further. Measuring blood flow changes during a vasodilatory stimulus is considered the most appropriate way to detect and quantify the vascular reserve. In this respect, impaired CVR has been found to correlate with an increased risk of ischemic cerebral events in subjects with carotid stenosis. We previously reported the existence of a relationship between hemodynamic impairment and diminished brain perfusion.

### Table 2. Comparison Among Estimated Marginal Means of MMSE Score Difference of Each Subgroup

<table>
<thead>
<tr>
<th>Variable (I) (Mean MMSE Difference)</th>
<th>Variable (J) (Mean MMSE Difference)</th>
<th>( I - J )</th>
<th>SE</th>
<th>P Value</th>
<th>95% CI (Difference)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHI: bilaterally normal (0.894; 95% CI, 0.521–1.268)</td>
<td>BHI: right pathological</td>
<td>–0.891</td>
<td>0.325</td>
<td>0.007</td>
<td>–1.533</td>
<td>–0.249</td>
<td></td>
</tr>
<tr>
<td>BHI: right pathological (1.786; 95% CI, 1.275–2.297)</td>
<td>BHI: left pathological</td>
<td>–0.729</td>
<td>0.337</td>
<td>0.032</td>
<td>–1.394</td>
<td>–0.063</td>
<td></td>
</tr>
<tr>
<td>BHI: right pathological (1.623; 95% CI, 1.071–2.175)</td>
<td>BHI: right pathological</td>
<td>–0.163</td>
<td>0.387</td>
<td>0.675</td>
<td>–0.927</td>
<td>0.602</td>
<td></td>
</tr>
<tr>
<td>BHI: right pathological (3.067; 95% CI, 2.643–3.490)</td>
<td>BHI: right pathological</td>
<td>1.281</td>
<td>0.338</td>
<td>0.0001</td>
<td>0.614</td>
<td>1.948</td>
<td></td>
</tr>
</tbody>
</table>

BHI indicates breath-holding index; CI, confidence interval; I, mean of the first column; J, mean of the second column; and MMSE, Mini-Mental State Examination.
function in specific cognitive domains in patients with carotid stenosis, in the absence of otherwise clinically expressed ischemic events. The risk of cognitive deterioration in patients with carotid stenosis has been extensively evaluated, but the results have supported equivocal evidence. In particular, there are controversies about the interpretation of the presence of impaired mental performances. Some studies have suggested that cognitive dysfunction rather than being a consequence of the carotid disease may be directly related to the brain ischemic damage. There is also evidence suggesting that reduction in mental performance in patients with carotid steno-occlusive disease may be a nonspecific consequence of a generalized vascular disease. Accordingly, cognitive impairment would be one of the results of brain dysfunction related to the underlying vascular risk factors, such as hypertension and diabetes mellitus.

Findings from the present study support the possibility that a reduction in cognitive performances in subjects with carotid stenosis could be more likely related to the hemodynamic consequences of chronic hypoperfusion rather than being reflective of a generalized atherosclerotic disease. Carotid IMT is a marker of atherosclerosis that is able to characterize global vascular risk. The fact that in our patients increased IMT was not able to predict reduction in MMSE score argues against the hypothesis that cognitive deterioration in subjects with steno-occlusive carotid disease may be simply considered as a consequence of atherosclerotic status.

Improvement of pharmacological approaches for treating vascular risk factors has produced significant changes in the management of patients with asymptomatic severe carotid stenosis. In particular, the indication for surgical or endovascular correction of the artery lumen narrowing for primary stroke prevention in asymptomatic carotid disease is generally limited to selected individual cases, where pharmacological and lifestyle change interventions do not result as optimal strategies.

Considering cognitive decline as a specific consequence of carotid disease is a relatively new concept, and carotid steno-occlusive disease has been recently identified as one of the vascular risk factors that can be modified through an appropriate clinical strategy to prevent or reduce cognitive impairment. Early selection of subjects deserving consideration for revascularization procedures or pharmacological treatments able to improve cerebral hemodynamics would have an important role in planning more effective primary prevention approaches. The presence of hemodynamic insufficiency in carotid steno-occlusive disease should be detected before significant loss in neurological function develops, especially in complex conditions, such as in the case of bilateral carotid stenosis. This concept is also supported by the evidence that in subjects with cerebrovascular occlusive disease but without clinical or imaging evidence of previous cerebral infarctions, a relationship between exhaustion of cerebrovascular reserve and cortical thickness has been established. This anatomic alteration seems to be, at least partially, reversible after surgical revascularization. Our study has several limitations. To evaluate cognitive performance, we used the MMSE that is usually considered as a screening test of global cognitive function. It is possible that MMSE was not refined enough to detect changes in mental performances in apparently asymptomatic subjects fully. However, MMSE is the most commonly used cognitive evaluation and, in a longitudinal study design, preliminary exploration using a screening test can be regarded as sufficiently adequate to generate hypothesis and to stimulate further investigation on this matter. In this respect, a more comprehensive and standardized neuropsychological assessment in subjects with carotid stenosis is required in future studies to obtain stronger evidences about the link between hemodynamic impairment and cognitive decline. It has been suggested that serial evaluations using tests, such as the Montreal Cognitive Assessment or the Addenbrooke’s Cognitive Examination-Revised, might allow to overcome specific limits intrinsic to each individual test, for example, the habit effect, and the low sensitivity of the MMSE in the identification of mild cognitive disturbances.

Our investigation did not include a neuroimaging evaluation. For this reason, it is not possible to establish the contributory role of white matter lesions, silent infarcts, and brain atrophy occurrence in the development of a reduction of cognitive performances in our population. Nonetheless, previous evidences suggested that high-grade stenosis of the ICA may promote cognitive impairment even without neuroimaging evidence of brain structural changes. Our study consisted of a 1-time evaluation of CVR, carotid IMT, and stenosis, and, therefore, was not possible to evaluate how the progression of these parameters over time could affect cognitive performance. Unfortunately, a follow-up evaluation of CVR, carotid IMT, and stenosis was proved unfeasible given the low compliance rate to the BH test performance in the group of patients who presented during the study period a significant cognitive deterioration. The low compliance with voluntary apnea in these subjects would have generated data not comparable with those obtained at baseline.

With our experimental approach, we were able to suggest new insights on the risk carried by patients with bilateral carotid severe stenosis. The presence of a cognitive deterioration in a subgroup of subjects and the significant influence of impaired CVR suggest that in the presence of a severe vascular condition, such as a bilateral carotid stenosis, it is possible to identify patients at increased risk of developing unfavorable clinical outcomes.

Our findings further underline the need to include assessment of cognitive performance when evaluating subjects with apparently asymptomatic carotid stenosis to understand risk–benefit ratio of different treatment strategies better. In this perspective, detection of cerebral hemodynamic impairment may contribute to select subjects at the highest risk of developing cognitive deterioration.

Disclosures

None.

References


Cognitive Deterioration in Bilateral Asymptomatic Severe Carotid Stenosis
Laura Buratti, Clotilde Balucani, Giovanna Viticchi, Lorenzo Falsetti, Claudia Altamura, Emma Avitabile, Leandro Provinciali, Fabrizio Vernieri and Mauro Silvestrini

*Stroke*. 2014;45:2072-2077; originally published online June 5, 2014; doi: 10.1161/STROKEAHA.114.005645

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/45/7/2072

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/12/29/STROKEAHA.114.005645.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/
无症状性双侧颈动脉重度狭窄与认知恶化

Cognitive Deterioration in Bilateral Asymptomatic Severe Carotid Stenosis

Laura Buratti, MD; Clotide Balucani, MD; Giovanna Viticchi, MD; Lorenzo Falsetti, MD; Claudia Altamura, MD; Emma Avitabile, MD; Leandro Provinciali, MD; Fabrizio Vernieri, MD; Mauro Silvestrini, MD

背景和目的: 本研究旨在观察无症状性双侧颈动脉重度狭窄患者的认知功能, 以探讨脑血流动力学及颈动脉狭窄性疾病的潜在影响。

方法: 本研究纳入意大利双侧颈内动脉重度狭窄的患者, 并对其进行了为期 3 年的随访研究。登记患者的背景资料、吸烟史、饮酒史及药物治疗情况。所有患者均接受了彩色多普勒超声检查, 以确定颈内动脉狭窄的严重程度及血流速度。

结果: 在随访期间, 无症状性双侧颈动脉重度狭窄的患者可能出现认知功能障碍, 特别是记忆力、注意力及空间定向能力的下降。研究人员采用经颅多普勒超声检查评估患者颈动脉的血流速度及搏动指数, 并利用简易精神状态检查评估患者的认知功能。

结论: 无症状性双侧颈动脉重度狭窄的患者可能出现认知功能障碍, 需要定期进行超声检查以便及早发现并采取预防措施。
双侧或单侧颈动脉硬化症的临床认知障碍

最近的一项研究显示，双侧颈动脉硬化症患者在认知功能方面的表现可能较轻[19]。因此，研究者建议在评估这些患者的认知功能时，应该考虑双侧颈动脉硬化症的影响。此外，BHI（屏气指数）的变化可能有助于评估认知功能的变化。

### 结果

对这200例双侧颈动脉硬化症患者进行了回顾性分析。首先，我们对这些患者的BHI进行了统计分析。然后，我们对这些患者的BHI进行了对数转换，以便评估其与认知功能的变化。最后，我们对这些患者的BHI进行了线性回归分析，以评估其与认知功能的变化。

### 讨论

本研究的目的是探讨BHI的变化对认知功能的影响。我们发现，BHI的变化对认知功能的影响是显著的。此外，我们还发现，BHI的变化对认知功能的影响可能是由于其与脑血管储备功能的密切关系。因此，我们建议在评估这些患者的认知功能时，应该考虑BHI的变化。
管储备功能的耗竭与皮质厚度具有相关性，这一结论亦支持上述观点。

狭窄。在既往无临床或影像学中确定脑梗死的脑血管闭塞患者中，脑血
流的一级预防措施。颈动脉狭窄或闭塞性疾病中的脑血流动力学异常应
寻求经性患者的治疗前缺乏前被发现，尤其是在复杂情况下。如解除脑动脉
狭窄，在既往未或影像学中确定脑梗死的脑血管闭塞患者中，除了血
管储备功能的耗竭与皮质厚度具有相关性，这一结论亦支持上述观点。

研究在一些临床上，我们采用了用于评估整体认知功能的 MMESE 测量。而 MMESE 可以不考虑性检测出无法识别需要表
的判断。然而，MMESE 作为最广泛的应用一种认知工具。研究
列研究进行计算机，以及在工具进行的疼痛以及睡眠状况的理论。有
研究认为，运用 MMESE，如 MMSE、表 A-8、量表，可能需要去
指一些临床上的多样性。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。

研究采用一种神经学质量，因为它们不能独立于中段，无症状性
障碍及研究是否对认知功能有影响。然而，研究采用 MMESE 作为评估整体认知功能的度量。