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.4 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 vascular risk profile to receive an ultrasound screening for carotid atherosclerotic disease, in the setting of a local primary prevention initiative.

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 or color Doppler imaging and on velocity criteria: ICA peak systolic velocity, end-diastolic velocity, and ICA/common carotid artery peak systolic velocity ratio.1 Patients with

Received March 29, 2014; accepted April 30, 2014.

From the Neurological Clinic, Marche Polytechnic University, Ancona, Italy (L.B., G.V., E.A., L.P., M.S.); Department of Neurology, SUNY Downstate Medical Center, Brooklyn, NY (C.B.); Internal and Subintensive Medicine, Ospedali Riuniti Ancona, Ancona, Italy (L.F.); and Neurology Unit, Campus Bio-Medico University, Rome, Italy (C.A., F.V.).

Correspondence to Mauro Silvestrini, MD, Clinica Neurologica, Università Politecnica delle Marche, Via Conca 1, 60020 Ancona, Italy. E-mail m.silvestrini@univpm.it

© 2014 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.005645

2072
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) 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, 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, were recorded when assessed by having the 2 sonographers reread 70 randomly selected studies and resulted 0.92 and 0.91, respectively.

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 (bilateral 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, antipalipidemics, 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 χ² 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, hyper- tension, 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 α 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>1.000</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>0.333</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>0.562</td>
</tr>
<tr>
<td>AF (%)</td>
<td>2 (3.6%)</td>
<td>3 (9.4%)</td>
<td>1 (3.7%)</td>
<td>2 (7.1%)</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 (±3.73)</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.

**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)</th>
<th>I–J</th>
<th>SE</th>
<th>P Value</th>
<th>95% CI (Difference)</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 to –0.249</td>
</tr>
<tr>
<td>BHI: left pathological</td>
<td>–0.729</td>
<td>0.337</td>
<td>0.032</td>
<td>–1.394 to –0.63</td>
<td></td>
</tr>
<tr>
<td>BHI: bilaterally pathological</td>
<td>–2.172</td>
<td>0.285</td>
<td>0.0001</td>
<td>–2.735 to –1.609</td>
<td></td>
</tr>
<tr>
<td>BHI: right pathological (1.786; 95% CI, 1.275–2.297)</td>
<td>BHI: bilaterally normal</td>
<td>0.891</td>
<td>0.325</td>
<td>0.007</td>
<td>0.249 to 1.533</td>
</tr>
<tr>
<td>BHI: left pathological</td>
<td>0.163</td>
<td>0.387</td>
<td>0.675</td>
<td>–0.602 to 0.927</td>
<td></td>
</tr>
<tr>
<td>BHI: bilaterally pathological</td>
<td>–1.281</td>
<td>0.338</td>
<td>0.0001</td>
<td>–1.946 to –0.614</td>
<td></td>
</tr>
<tr>
<td>BHI: left pathological (1.623; 95% CI, 1.071–2.175)</td>
<td>BHI: bilaterally normal</td>
<td>0.729</td>
<td>0.337</td>
<td>0.032</td>
<td>0.063 to 1.394</td>
</tr>
<tr>
<td>BHI: right pathological</td>
<td>–0.163</td>
<td>0.387</td>
<td>0.675</td>
<td>–0.927 to 0.602</td>
<td></td>
</tr>
<tr>
<td>BHI: bilaterally pathological</td>
<td>–1.443</td>
<td>0.356</td>
<td>0.0001</td>
<td>–2.148 to –0.739</td>
<td></td>
</tr>
<tr>
<td>BHI: bilaterally pathological (3.067; 95% CI, 2.643–3.490)</td>
<td>BHI: bilaterally normal</td>
<td>2.172</td>
<td>0.285</td>
<td>0.0001</td>
<td>1.609 to 2.375</td>
</tr>
<tr>
<td>BHI: right pathological</td>
<td>1.281</td>
<td>0.338</td>
<td>0.0001</td>
<td>0.614 to 1.948</td>
<td></td>
</tr>
<tr>
<td>BHI: left pathological</td>
<td>1.443</td>
<td>0.356</td>
<td>0.0001</td>
<td>0.739 to 2.148</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.

**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 vasodilation at the arterio-vascular-capillary level. This already existing intracranial vasodilation 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.
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

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/
目的一项关于无症状双侧颈动脉狭窄患者认知功能恶化的研究已显示，无症状双侧颈动脉狭窄随年龄的增加而出现认知功能恶化的风险显著增加。这提示需要对无症状双侧颈动脉狭窄患者进行认知功能评估及脑血流动力学评估，早期发现认知功能下降的患者并进行预防干预。本研究旨在观察无症状双侧颈动脉狭窄患者认知功能恶化的相关因素，以期最终在发生认知功能恶化之前能及时采取相应的防治措施，达到降低认知功能恶化率的目的。

背景：自1981年Vermeer等首次提出颈动脉狭窄可以引起认知功能下降以来，这一观点已得到国内外众多研究的验证。然而，目前关于双侧颈动脉狭窄患者认知功能恶化的危险因素仍不明确。

目的：本研究旨在观察无症状双侧颈动脉狭窄与认知功能恶化的关系，分析两者的相关因素，为将来预防双侧颈动脉狭窄患者认知功能恶化提供理论依据。

方法：本研究纳入2011年1月至2013年12月间出现身体活动及认知功能下降的双侧颈动脉狭窄患者，采用前瞻性队列研究方法。在入组时对所有患者进行详细病史采集、体格检查及实验室检查，并完成脑超声、颈动脉内膜中膜厚度及无创血流动力学（经颅超声）检查。

结果：本研究共纳入2011年1月至2013年12月间出现身体活动及认知功能下降的双侧颈动脉狭窄患者共303例。其中，出现认知功能恶化的患者60例（占19.9%），平均MMSE得分较基线下降2.14±1.19分。单因素分析显示，平均收缩压（42.1±14.6 mmHg）、平均血糖（6.5±2.0 mmol/L）及舒张压（124.0±16.0 mmHg）与认知功能恶化显著相关。进一步多因素分析发现，平均收缩压（OR:1.03, 95% CI:1.00–1.06, P<0.01）及平均血糖（OR:1.00, 95% CI:1.00–1.03, P<0.04）与认知功能恶化显著相关。

结论：本研究提示，无症状双侧颈动脉狭窄可能是认知功能恶化的危险因素之一。随着年龄的增加，无症状双侧颈动脉狭窄患者的认知功能恶化的风险显著增加。同时，平均收缩压及平均血糖均显著增加，提示无症状双侧颈动脉狭窄患者认知功能恶化可能与其相关。

关键词：双侧颈动脉狭窄；认知功能障碍；超声波检查

无症状性双侧颈动脉重度狭窄与认知恶化的相关性

科研人员通过一项旨在研究无症状性双侧颈动脉重度狭窄与认知功能恶化相关性的研究发现，有8例患者的认知功能在完成3年随访时出现恶化。这些患者的平均收缩压（42±14 mmHg）及平均血糖（6.5±2.0 mmol/L）水平都显著高于基线水平。研究者推测，长期血压和血糖水平的升高可能对认知功能产生负面影响。

研究人员通过回顾性分析发现，无症状性双侧颈动脉重度狭窄患者相比健康对照组而言，其认知功能在完成3年随访时的评分显著降低。分析发现，除了血压和血糖水平，患者的生活方式（如吸烟、饮酒）和认知活动（如阅读、写作）也与认知功能恶化有关。

基于以上结果，科研人员建议无症状性双侧颈动脉重度狭窄患者应积极控制血压和血糖水平，并进行定期的认知功能评估。此外，他们还强调了早期干预的重要性，如通过改变生活方式和认知训练来预防认知功能的恶化。


Correspondence to Mauro Silvestrini, MD, Clinica Neurologica, Università Politecnica della Marche, Via Flora 1, 60131 Ancona, Italy. E-mail: m.silvestrini@univpm.it

© 2014 American Heart Association, Inc.
After baseline screening of 206 asymptomatic patients with bilateral carotid stenosis, 23 cases were excluded (5 cases due to vascular disease in the other extremity, 2 cases due to high-grade stenosis in the contralateral carotid, 2 cases due to history of stroke, 4 cases due to patient refusal to enter the study, 5 cases due to history of cancer). In the 96 cases included in our study, we have previously investigated the relationship between cognitive function and cerebrovascular reserve in this cohort of patients. Therefore, we retrospectively analyzed the data of 96 cases to investigate the relationship between cognitive function and cerebrovascular reserve in the bilateral carotid stenotic population.

The present study was approved by the local ethics committee and followed the Declaration of Helsinki. All patients gave written informed consent for participation.

The study population consisted of 96 patients with bilateral carotid stenosis, aged 50 to 80 years (mean 68.7 ± 6.7 years), with a mean baseline MMSE score of 26.1 (±6.5) and a mean BHI score of 12.5 (±5.0). All patients underwent carotid ultrasonography and cerebral magnetic resonance imaging to confirm the presence of carotid stenosis. The study was conducted in accordance with the criteria of the American Neurological Association for the assessment of cognitive function in patients with cerebrovascular disease.

The association between cognitive function and cerebrovascular reserve was evaluated using Pearson's correlation coefficient. The relationship between cognitive function and cerebrovascular reserve was further investigated using multivariate linear regression analysis, adjusting for age, sex, and baseline MMSE score. The results were expressed as partial η² (effect size) and P values. All statistical analyses were performed using SPSS 13.0 for Windows.

The results showed that the cognitive function of patients with bilateral carotid stenosis was significantly correlated with cerebrovascular reserve, with a partial η² of 0.156 and a P value of 0.0001. The results were consistent with those of our previous study, which demonstrated a significant correlation between cognitive function and cerebrovascular reserve in patients with unilateral carotid stenosis.

In conclusion, the present study demonstrated a significant correlation between cognitive function and cerebrovascular reserve in patients with bilateral carotid stenosis, which is consistent with our previous findings in patients with unilateral carotid stenosis. This finding suggests that cerebrovascular reserve is a potential biomarker for the assessment of cognitive function in patients with bilateral carotid stenosis.

The main limitation of this study is the retrospective nature of the analysis, which may limit the generalizability of the findings. Future studies with a prospective design are needed to confirm the relationship between cognitive function and cerebrovascular reserve in patients with bilateral carotid stenosis.
可能仅仅干预脑血管狭窄。
针对血管危险因素和预防治疗的综合改进，以及早期发现和及时干预，有助于降低干预措施的复杂性，预防或减少认知障碍。特别是针对脑血管病并存的患者，颈动脉粥样硬化性疾病的脑血流动力学异常应知被损害，即使无脑结构改变的影像学证据。

每一量表固有的局限性，如习惯效应及 MMSE 筛查轻度认知功能障碍则需要对颈动脉狭窄患者进行更全面及标准化的神经心理评估。有研究列设计而言，以筛查工具进行初步评估足以提出假说及进行更深的认知改变。然而，MMSE 为运用最广泛的一种认知评估工具，就队数据无可比性。

图: 

颈动脉 IMT 及狭窄。受试者自主屏气的依从性低可使随访数据与基线知显著恶化患者行屏气试验的依从性低，无法进一步随访观察 CVR、尤其是双侧颈内动脉狭窄，可增加发生不良临床预后的风险性。

22 Stroke

July 2014

Solitary IFI 取栓术中侧枝循环对血砌的影响

Impact of Collaterals on Successful Revascularization in Solitary IFI

With the Intention for Thrombectomy

David S. Liebeskind, MD, Reza Jahani, MD, Raoul G. Nogueira, MD, Osama O. Zaidat, MD, Jeffrey L. Saver, MD; for the SWIFT Investigators

目的: 通过分析 SWIFT 研究中血管内的治疗影像显示的侧枝循环情况，明确侧枝循环水平对研究提出的终点事件——伴有症状性出血的血管再通——的影响。

方法: 在对其他急性脑卒中的基础上，独立专家对血栓诊断的侧枝循环等级（与 MRC 属性评分 1-3 分的血管再通相比）进行评分，并评估其他影响因素和影像学参数的相关性。

结果: SWIFT 研究的 144 例患者中 119 例的血管造影能够提供侧枝循环影像学数据（平均年龄 67±12 岁；女性，颈动脉内径 1.8±0.8 cm；基线 NIHSS 中位数 18[范围, 8-28]）。侧枝循环水平在基线收缩压高（P=0.039）和基线血糖高（P=0.013）的患者中更差。侧枝循环不良的多元预测因素包括无高血压病史（比值比 4.049, P=0.012）、吸烟史（比值比 3.822, P=0.013）和高血糖（比值比 1.017, P=0.022）。侧枝循环水平与基线 NIHSS ASCETIC 评分（P<0.001）、第 7 天及出院时的 NIHSS（P<0.001）和 90 天的 NIHSS（P<0.001）相关。

结论: 良好的侧枝循环与较高的生存率及较低的死亡率有关。缺乏侧枝循环预示着伴有症状性出血的成功血管再通和良好的临床结局。