ORIGINAL ARTICLE

COGNITIVE AND BALANCE IMPROVEMENT AFTER CAROTID ENDARTERECTOMY IN ASYMPTOMATIC PATIENTS: A PROSPECTIVE STUDY

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Abstract

Introduction: *Recent studies proved impaired cognition, mobility and balance in patients with significant asymptomatic carotid stenosis (ACAS) in comparison to general adult population. In our study, we tested the hypothesis that patients with severe ACAS (≥70% diameter-reducing stenosis) would have long-term cognitive, mobility and balance improvement after carotid revascularization.*

Methods: *All asymptomatic patients who underwent carotid endarterectomy from a 20-month period in our institution were prospectively enrolled. Cognitive, mobility and balance tests were performed the week before surgery and had post-operative re-evaluation at 6-8 months. Executed tests were Mini-Mental State Exam (MMSE), Timed Up and Go test (TUG), 2 Minute Walk Test (2MWT), Berg Balance Scale (BBS) and Activities-specific Balance Confidence (ABC) Scale.*

Results: *18 patients were recruited. The mean age was 70.11±7.29 years, 72.22% were man, 44.44% had severe unilateral stenosis and the remaining bilateral stenosis. Patients had impaired scores at baseline, ranging from 11.11% to 44.44%. Post-operative upgrading in absolute score was noted in all tests ($p<.021$) except TUG, and greatest improvement in the percentage of compromised scores was noted in BBS (relative risk 6.6, $p=.025$). A strong negative correlation was verified between several baseline absolute scores and the level of postoperative variation ($r=-0.87$ for MMSE, $r=0.80$ for TUG and $r=0.82$ for BBS with $p<.001$, and $r=0.52$ for ABC with $p=.032$).*

Conclusion: *Carotid endarterectomy improved balance and cognition in a group of asymptomatic patients with severe carotid stenosis. Greatest improvements were noted in dynamic movement tests with most reduced scores at baseline.*

Keywords: *asymptomatic carotid stenosis, carotid endarterectomy, cognitive, balance, mobility.*

INTRODUCTION

Asymptomatic carotid stenosis (ACAS) occurs in 4.2% of the adult population, with an estimated prevalence of 12.5% in man and 6.9% in woman ≥70 years-old[1]. So far, prevention of stoke has been the main focus of asymptomatic carotid stenosis medical and surgical management, and international orientations for carotid endarterectomy (CEA) recommend surgery in selected groups of asymptomatic patients with increased risk of stroke in the future[2].

Recently, interest has grown regarding cognitive performance and motility function in patients with carotid stenosis and cerebral hypoperfusion. Studies shown a decline in cognitive capacity in 34% of the patients with significant carotid stenosis over 5 years[3] and a 2.4-5.0 increased risk of developing dementia comparing with patients with no carotid stenosis[4]. Memory and processing fluency were specially compromised in patients with moderate and severe stenosis[5,6]. Possible described causes for cognitive dysfunction in ACAS include asymptomatic brain emboli or stroke, white-matter lesions and mainly a decrease in cerebral perfusion[7]. Latest, a reduction in mobility and physical function and balance has also been described in asymptomatic carotid stenosis, with higher limitations in patients with severe stenosis[8]. A significant 2.86 higher risk of falls was detected in this group[8].

In fact, cognitive dysfunction and motility impairment frequently coexist in older people[9]. Cognitive function, motility and balance are determinant factors for independent living as opposed to disability, frailty, risk of falls, institutionalization and death in the old population[10,11]. These data raise the concern that ACAS might not be a minor disease, but could have major implications in quality of life, with a gradual decrement in physical and mental capacity due to cerebral flow restriction, even in patients with no past history of stroke.

Since cognitive domain, mobility and balance are compromised in people with carotid stenosis, there is a hypothesis that all these functions might suffer alterations after carotid revascularization. Therefore, the objective of our prospective study was to evaluate if cognition, mobility and balance might improve in a long-term after CEA in patients with severe asymptomatic carotid stenosis (with unilateral or bilateral ≥70% diameter-reducing stenosis).

MATERIALS AND METHODS

Subjects

We prospectively identified all asymptomatic patients submitted to carotid endarterectomy of a central referral hospital for vascular surgery in Portugal, from October 2020 to June 2021. Inclusion criteria included patients ≥18 years-old, patients with no previous stroke or previous neurologic event > 6 months ago with Rankin 0 to 2 and complete clinical recovery, elective surgery and unilateral or bilateral severe stenosis ≥70%. Patients with significant intracranial stenosis, previous ipsilateral carotid artery surgery, previously diagnosed non-vascular dementia (such as Alzheimer disease), neuropsychiatric diseases or confusion/altered consciousness who cannot cooperate, and limiting physical impairment that precluded motility tests were excluded.

Surgery and Cognitive/ Motility/ Balance Tests

Surgical indication for asymptomatic high-risk severe carotid stenosis with plaque instability, stenosis progression or silent ipsilateral infarction was according to guidelines2 and was not influenced by the study. All patients received antiplatelet therapy and had cardiovascular risk factor modification therapy before surgery. Degree of carotid stenosis was defined according to the North Symptomatic Carotid Endarterectomy Trial (NASCET) criteria[12]. Pre-operative evaluation included cervical and cranial computed tomography angiography and post-operative ultrasound was performed by a certified vascular surgeon at the time of post-operative tests reevaluation. CEA was performed under continuous electroencephalography monitoring. There was a preference in the department for eversion or partial eversion technique.

Cognitive, mobility and balance tests were performed by two experienced physicians 1-3 days before surgery and patients were re-evaluated at 6-8 months after surgery. The most suitable scoring was attributed through mutual agreement.

Executed tests were Mini-Mental State Exam (MMSE), Timed Up and Go test (TUG), 2 Minute Walk Test (2MWT), Berg Balance Scale (BBS) and Activities-specific Balance Confidence (ABC) Scale. MMSE scale is scored 0-30 and includes 6 cognitive domains: orientation, timely memory, delayed memory, attention and computing power, language ability and visual-spatial perception[13]. Cognitive defect was considered according to the level of education: MMSE≤22 if ≤2 years education, MMSE≤24 if 3-6 years education and ≤27 if ≥7 years education. TUG requires rising from a chair, walking 3 meters, turning around, walking back and sitting down. A TUG score of ≥13.50 seconds was used to identify individuals at higher risk of falling[14]. 2MWT was used to calculate gait speed and classified as risk of frailty if <0.80m/s15 and dependency for daily activities if <0.55m/s16. BBS includes evaluates 14 static and dynamic activities for balance and functional motility of varying difficulty, with minimum score of 0 and best score of 5617. ABC is used

Table 1 **Characteristics of study participants according to unilateral or bilateral stenosis.**

Characteristics (n=18)	Unilateral Stenosis (n=8) (%, frequency)	Bilateral Stenosis (n=10) (%, frequency)	P-value*
Age (years; average±SD, range)	70.88±8.17 (58-80)	69.50±7.31 (59-83)	.63
Male gender	62.50% (5)	80.00% (8)	.42
Comorbidities			
Previous stroke/ TIA	87.50% (7)	60.00% (6)	.23
Hypertension	100.00% (8)	90.00% (9)	.42
Diabetes	37.50% (3)	40.00% (4)	.65
Dyslipidemia	75.00% (6)	70.00% (7)	.62
Obesity	25.00% (2)	0.00% (0)	.18
Smoking history	50.00% (4)	30.00% (3)	.35
Coronary disease	12.50% (1)	30.00% (3)	.38
PAD	12.50% (1)	10.00% (1)	.71

SD, standard deviation; TIA, transient ischaemic attack; PAD, peripheral artery disease. A p-value <.050 was considered statistically significant.
*Using Fisher's exact test or Mann-Whitney U test.

to evaluate perceived confidence to maintain balance under different daily circumstances on a scale of 0% (no confidence) to 100% (total confidence)18. Items to which the patient could not answer were not included in average score. Impaired balance was diagnosed using 14-item BBS if score <45 or ABC scale <80%. Significant change was considered for each test if alteration from impairment to normal score (and reverse) and in BBS if score difference ≥4 if baseline 45-56, ≥5 if baseline 35-44, ≥7 if baseline 25-34 and ≥5 if baseline 0-2417.

Statistical Analysis

Wilcoxon signed-rank test or 2-tailed t test were used to evaluate difference between baseline and post-operative results and 2-tailed McNemar's test to compare frequency of patients with pre-operative and post-operative impairment in each test. Histograms were used to address the number of patients in the impaired range in each test. Box and whisker plots were created for functions assessments at baseline and post-surgery.

Pearson's correlation was used to examine relationship between pre-operative scores and degree of post-operative cognitive and balance change. Logistic regression was used to identify confounding factors that could contribute to each test alteration.

Significant value was set at p-value <.050. Statistical analysis was performed using SPSS version 25.0 statistical software package®.

RESULTS

A total of 18 patients who were submitted to CEA with the above-mentioned criteria agreed to enrol the study. The mean age was 70.11±7.29 years, 72.22% were man, 44.44% had severe unilateral stenosis and the remaining had bilateral stenosis (half bilateral severe stenosis and half severe stenosis with contralateral moderate stenosis). No patient had contralateral occlusion. One patient was lost in follow-up.

Demographic and clinic data is described in Table 1. Most patients had low-level education with 3-6 years of schooling (83.3%, n=15), two patients had ≤2 years and only one patient ≥7 years of education. No post-operative strokes, death or myocardial infarction occurred in the participants. No carotid restenosis was identified in the post-operative evaluation.

MMSE, TUG, gait speed, BBS and ABC were applied the week before surgery and 6-8 months after intervention. Patients had altered scores at baseline according to the pre-stablished criteria, ranging from 11.11% to 38.89% depending on the evaluated test (Table 2). Greatest difference was noted in the fraction of impaired BBS score (38.89% patients with reduced scores at baseline versus 5.88% after surgery, p=.025). Pre-operative and post-operative absolute scores and their distribution are detailed in histograms in Figure 1 and boxplots in Figure 2. Statistical difference was noted between baseline and follow-up scores in the majority of the tests, except for TUG. No significant differences were noted between unilateral and bilateral stenosis groups in the characteristics of the participants and baseline scores (p>.18). Despite not having statistical significance, patients with evidence of past ipsilateral stroke (with or without symptoms) had tendency to lower absolute scores in mobility and balance baseline tests.

A strong correlation between lower baseline scores and the level of postoperative improvement was noted in cognitive, mobility and balance tests after calculation of Pearson coefficient (r=-0.87 for MMSE, r=-0.80 for TUG and r=-0.82 for BBS with p<.001, and r=-0.52 with p=.032 for ABC), Figure 3. Age and bilateral stenosis had no influence in tests scores or follow-up variation (p>.10). Masculine gender had some effect in the degree of postoperative improvement in tests MMSE (p=.001) and ABC (p=.005).

DISCUSSION

A significant percentage of patients with ACAS had decreased baseline scores in our search, mainly in mobility and balance scores (up to 38.89%), which is in line with previous publications[3,5-7]. And although frailty was not directly accessed

Table 2 **Proportion of patients with baseline and postoperative impairment in cognitive, mobility and balance tests.**

Tests	Patients with baseline impairment (n=18) (%)	Patients with postoperative impairment (n=17) (%)	P-value*
MMSE	11.11%	0.00%	.16
MMSE <28	44.44%	17.65%	.025
TUG	38.89%	35.29%	1.00
Gait speed	22.22%	17.65%	.32
BBS	38.89%	5.88%	.025
ABC	33.33%	23.53%	.32

MMSE, Mini-Mental State Exam; TUG, Timed Up and Go test; BBS, Berg Balance Scale; ABC, Activities-specific Balance Confidence Scale. A p-value <.050 was considered statistically significant.
*Using 2-tailed McNemar test.

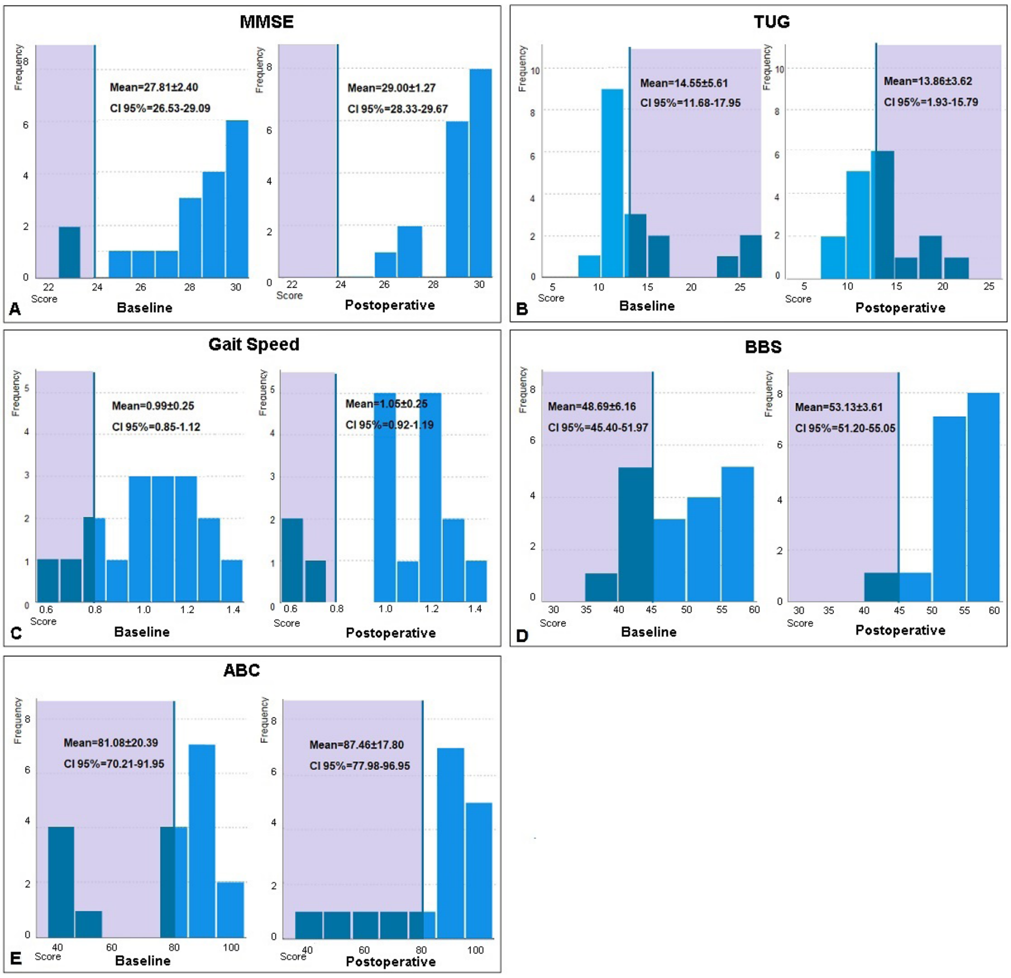

Figure 1 *Histograms indicating baseline and postoperative absolute scores in cognitive, mobility and balance tests in patients with high-grade asymptomatic carotid stenosis. Mean and 95% CI (confidence interval) are indicated. A. MMSE, Mini-Mental State Exam. B. TUG, Timed Up and Go test. C. Gait speed (m/s). D. BBS, Berg Balance Scale. E. ABC, Activities-specific Balance Confidence Scale.*
The shadow area in each graphic represents impaired scores. Despite cognitive defect was set according to level of education, the two patients with impaired MMSE scores had 3-6 years of education, so a 24-point score was used as cutoff in histogram A.

in our study, four of the 18 patients had initial gait speed <0.8m/s, which is compatible with risk of frailty and disability. Published studies describe decreased cognitive and functional scores in more severe stenosis in comparison to moderate stenosis or no stenosis. In our investigation we only included patients with severe stenosis and no statistically significant difference was noted between baseline scores of patients with unilateral or bilateral carotid stenosis (p>.20).

In our research, only two patients had baseline cognitive defect according to scholarity level. While MMSE is the most used single cognitive evaluation test[18], it might have low sensitivity and not detect minor cognitive alterations. In retrospective, most exhaustive tests such as Montreal Cognitive Assessment (MoCA) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) could have been more adequate to detect minor alterations[19,20]. Tests TUG, gait speed and subjective test ABC might also not be sensitive enough to detect slight limitations.

The fact that a few patients were recruited could have limited significance. Moreover, no control group was included. Restraining patients with severe ACAS and surgical indication from surgery would have been unethical, though.

Overall, in our study we verified an improvement in cognition, motility and balance absolute scores after carotid endarterectomy in patients with severe ACAS in post-operative evaluation (baseline average MMSE 27.81±2.40 versus postoperative 29.00±1.27, p=.007; baseline BBS 48.69±6.16 versus postoperative 53.13±3.61, p=.004; baseline ABS 81.08±20.39 versus postoperative 87.46±17.80, p=.003). This benefit was more evident in dynamic activities for balance, with a 6.6 times more impaired BBS scores (p=.025) and 1.4 times decreased ABC scores before surgery (p=.32). We also noticed a propensity to better MMSE scores post-operatively (baseline cognitive deficit in 11.11% versus postoperative 0.00%, p=.157; baseline MMSE<28 in 44.44% versus postoperative 17.65%, p=.025).

Moreover, improvement correlated strongly with baseline deficit (r=-0.80 for TUG and r=-0.82 for BBS with p<.001, r=-0.52 with p=.032 for ABC). Likewise, people with previous cognitive deficit had upgrading after

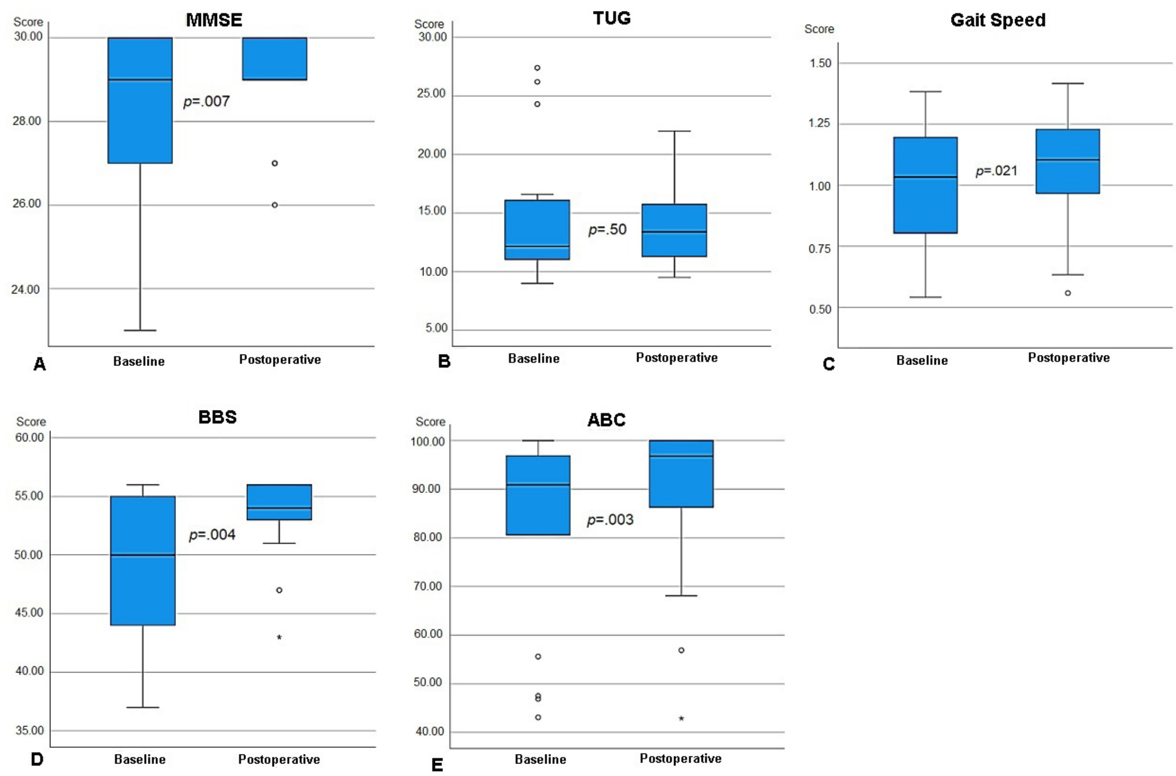

Figure 2

Boxplots representing baseline and postoperative absolute scores in cognitive, mobility and balance tests in patients with high-grade asymptomatic carotid stenosis. A. MMSE, Mini-Mental State Exam. B. TUG, Timed Up and Go test. C. Gait speed (m/s). D. BBS, Berg Balance Scale. E. ABC, Activities-specific Balance Confidence Scale.
Horizontal line in boxplot indicates the median, top line in boxplot the 75th percentile, bottom line in boxplot the 25th percentile and extremity whiskers the minimum and maximum values. Outliers are marked with small circles. A p-value <.050 was considered statistically significant. P-value was calculated using Wilcoxon Signed Rank Tests or 2-tailed t tests.

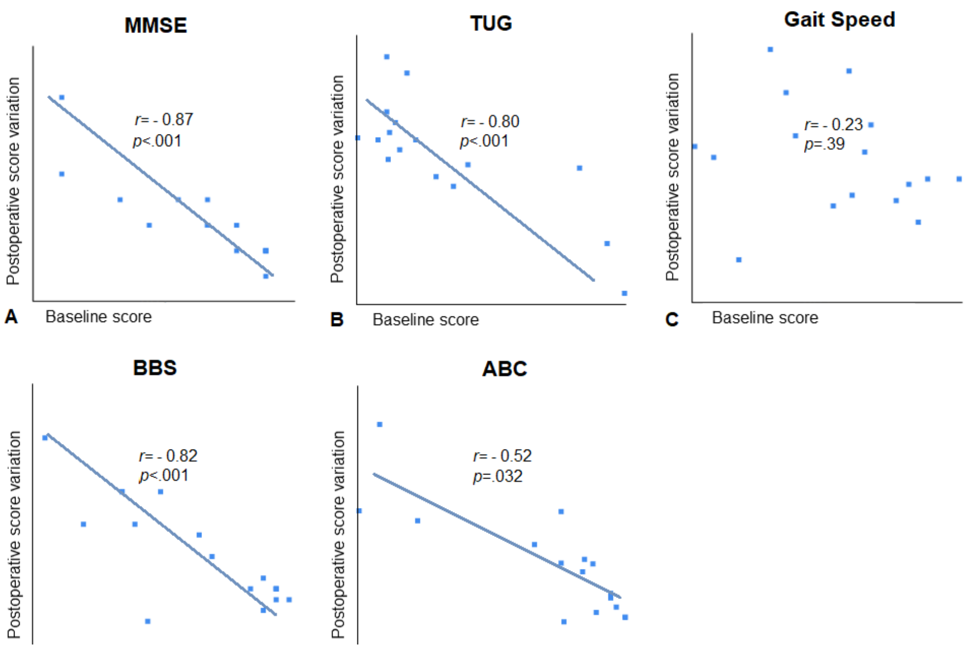

Figure 3

Graphics demonstrating relationship between the level of variation in each cognitive, mobility and balance test score after carotid endarterectomy according to baseline score using Pearson correlation. A. MMSE, Mini-Mental State Exam. B. TUG, Timed Up and Go test. C. Gait speed. D. BBS, Berg Balance Scale. E. ABC, Activities-specific Balance Confidence Scale.
A p-value <.050 was considered statistically significant.

revascularization (r=-0.87, p<.001). Our results confirm that post CEA, cognition, motility and balance improvements might persist long-term and raises the possibility that patients with pre-operative compromised cognition and balance could benefit from carotid surgery. Improvement in tests through learning mechanism seems unlikeable since patients were revaluated once at 6-8 months.

Similar to our findings, some publications described a late improvement in cognitive functions 3-6 months after carotid revascularization[19,21-23], especially in patients with previous cognitive dysfunction[21-23]. A systematic review described improvement in one or two cognitive tests in ACAS in only 24.8% of the patients[24] and cognitive enhancement was independent of revascularization technique with stent or CEA[23,25].

Gray et al[26] published the only study that evaluates balance and dynamic mobility after carotid revascularization. Twenty ACAS patients were reevaluated 6-weeks after carotid surgery and in similarity with our findings, they described a significative improvement in Dynamic Gait Index and Mini-Balance Evaluation Systems Test (Mini-BESTest), especially in patients with reduced pre-operative scores. These results were validated by the recent Miyake and colleagues[27] prospective research. In this recent publication with 50 patients, the authors correlated impaired supratentorial cerebral blood flow with a lower vestibulo-ocular reflex, and both dizziness and these markers significantly improved after carotid revascularization.

Since some patients with severe stenosis have preserved intracranial flow, diminished brain perfusion might be explained by diminished cerebrovascular reserve with impaired compensatory vasodilation in intracranial arterioles in patients with carotid stenosis[6]. Lattanzi et al[28] associated cognitive improvement at 6 months with ipsilateral compromised vasomotor reactivity before CEA. Whooley et al[29] found that only patients with important increase in middle cerebral artery (MCA) flow had significant cognitive improvement after surgery. This capacity to enhance cerebral flow after revascularization might have some implication in post-operative remodelling. Similarly, Porcu et al[30] affirmed better interhemispheric and cerebellar connections after carotid revascularization, and Zhang et al[31] correlated better post-operative cognition with growing bilateral thalamic and basal ganglia volume, perhaps due to increased perfusion and enhanced neuronal activity.

All the above-mentioned results support the fact that since cognition, mobility and balance functions share central mechanisms and are controlled by similar regions in the brain (including frontal cortex and subcortical nuclei), upgrading in brain perfusion might alter simultaneously these functions, especially in patients with impaired brain reserve. In fact, compromised vasomotor reactivity was considered a high-risk factor for late stroke in patients with severe ACAS in last European guidelines[2] and a potential factor to consider carotid revascularization in this group of patients. And besides we did not measure the cerebral vascular reserve in our study, this theory could help explain post-operative improvement in a selected group of patients.

To conclude, asymptomatic carotid stenosis might be an insidious disease with increased risk of cognitive, mobility and balance dysfunction and consequently autonomy limitation. Carotid revascularization can improve cognitive, mobility and balance, especially in a selected group of patients with previous limitations. Larger studies are needed to confirm our findings.

Conflicts of interest: no.
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