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**CEREBRAL HEMODYNAMICS
AND COGNITIVE PERFORMANCE
IN CAROTID ARTERY DISEASE**

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TABLE OF CONTENTS

TABLE OF CONTENTS	1
LIST OF ORIGINAL PUBLICATIONS	2
ABBREVIATIONS	3
SUMMARY	4
CHAPTER I	6
INTRODUCTION	6
<i>1.1 Atherosclerotic disease of internal carotid artery</i>	<i>6</i>
<i>1.2 Aims of the study</i>	<i>7</i>
CHAPTER II	8
MATERIALS AND METHODS	8
<i>2.1 Study participants</i>	<i>8</i>
<i>2.2 Cerebral hemodynamics assessment</i>	<i>9</i>
<i>2.3 Neuropsychological assessment</i>	<i>10</i>
<i>2.4 Statistical analysis</i>	<i>10</i>
CHAPTER III	12
RESULTS	12
CHAPTER IV	25
DISCUSSION	25
<i>4.1 Conclusion</i>	<i>28</i>
REFERENCES	29

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals (I-II).

- I. Lattanzi S, Carbonari L, Pagliariccio G, Bartolini M, Cagnetti C, Viticchi G, Buratti L, Provinciali L, Silvestrini M. Neurocognitive functioning and cerebrovascular reactivity after carotid endarterectomy. *Neurology*. 2018;90:e307-e315.
- II. Lattanzi S, Carbonari L, Pagliariccio G, Cagnetti C, Luzzi S, Bartolini M, Buratti L, Provinciali L, Silvestrini M. Predictors of cognitive functioning after carotid revascularization. *J Neurol Sci*. 2019 Aug 28;405:116435. doi: 10.1016/j.jns.2019.116435. [Epub ahead of print]

The thesis also contains some unpublished data.

ABBREVIATIONS

BH	Breath-holding
BHI	Breath-holding index
(ca)VF	Categorical verbal fluency
CEA	Carotid endarterectomy
CFCT	Complex Figure Copy Test
CPM	Coloured Progressive Matrices
CVR	Cerebral vasomotor reactivity
ICA	Internal carotid artery
MFV	Mean flow velocity
(ph)VF	Phonemic verbal fluency
TCD	Transcranial Doppler
TIA	Transient ischemic attack

SUMMARY

Background and aim: The inter-relationships between atherosclerotic disease of internal carotid artery (ICA), surgical revascularization and cognitive outcome are not fully understood. The aim of this study was to explore the relationship between cerebral hemodynamics and neurocognitive functioning in patients with high-grade ICA stenosis undergoing carotid endarterectomy (CEA).

Materials and methods: Patients with history of transient ischemic attack within the past 6 months and ipsilateral high-grade stenosis of ICA undergoing CEA were prospectively enrolled. Cerebral vasomotor reactivity (CVR) to hypercapnia was measured through transcranial Doppler ultrasonography. Coloured Progressive Matrices plus Complex Figure Copy Test, and phonemic plus categorical (ca) Verbal Fluency tests were performed to test cognitive functions of right and left hemispheres, respectively. Cerebral hemodynamics and cognitive functions were assessed before and 6 months after CEA.

Results: One hundred and eighty-three patients were included. The mean age was 73.1 (6.9) years and 122 (66.7%) were males. Before CEA, patients had decreased CVR on the side of ICA stenosis and reduced performance in the cognitive tests exploring the ipsilateral cerebral hemisphere. At 6 months from CEA, cerebral hemodynamics and neurocognitive functioning were significantly improved. The performance change in cognitive tests exploring the

revascularized hemisphere was inversely associated with pre-operative ipsilateral CVR and positively associated with the improvement in cerebral hemodynamics.

Conclusions: In patients with symptomatic high-grade ICA stenosis, cognitive performance was enhanced at 6 months since CEA. The cognitive improvement was related to the increase in CVR on the side of stenosis correction and predicted by baseline cerebral hemodynamic status. Cerebral hemodynamics may be an independent and potentially reversible determinant of cognitive dysfunction in severe carotid artery disease.

CHAPTER I

INTRODUCTION

1.1 Atherosclerotic disease of internal carotid artery

Extracranial carotid artery disease affects about 10% of subjects over 70 years, and its burden is expected to raise with the progressive aging of population. Being a recognized risk factor for stroke, transient ischemic attack (TIA) and cognitive impairment, it represents a growing public health issue.¹

Carotid endarterectomy (CEA) is currently recommended as secondary prevention of cerebral ischemia in patients presenting with stroke or TIA and ipsilateral moderate to severe internal carotid artery (ICA) stenosis.² Conversely, the influence of carotid revascularization on cognition still remains unclear.³

Cerebrovascular hemodynamic failure is one main mechanism of cognitive dysfunction in patients with atherosclerotic carotid disease, and the recovery of cerebral perfusion following ICA stenosis correction may have favorable effects. To date, however, the relationship between hemodynamic and cognitive changes following carotid revascularization have been not fully addressed and many questions remains unanswered.

1.2 Aims of the study

This study has been designed to explore the relationship between cerebral hemodynamics and neurocognitive functioning in patients with atherosclerotic ICA disease and evaluate the effects induced by surgical stenosis correction. To this end, cognitive performance and cerebrovascular reactivity have been assessed before and after surgery in patients with symptomatic high-grade ICA stenosis who underwent CEA.

CHAPTER II

MATERIALS AND METHODS

2.1 Study participants

Participants were patients who underwent CEA at the Vascular Surgery Unit of the Ospedali Riuniti of Ancona (Ancona, Italy) from January 2014 to December 2016, presented TIA within the past 6 months and had ipsilateral severe (70%-99%) ICA stenosis according to the North American Symptomatic Carotid Endarterectomy Trial criteria,⁴ as documented by noninvasive imaging. All patients underwent complete bloodwork, clinical history, neurologic and cardiologic examination, brain MRI, ECG, and transthoracic echocardiography before CEA.

Exclusion criteria were carotid occlusion, vertebrobasilar or intracranial stenocclusive disease, contralateral ICA stenosis $\geq 50\%$, cerebral infarct in the territory of stenotic ICA on neuroimaging, cardiac failure (left ventricular ejection fraction $< 50\%$), cardiac arrhythmia or other sources of cardiogenic embolism, history of stroke, any severe psychiatric disease, absence of temporal acoustic window/noncompliance with the cerebrovascular reactivity assessment with transcranial Doppler ultrasonography, and lefthandedness as by the Edinburgh Handedness Inventory.⁵

Age- and sex-matched controls were recruited in a 1:1 ratio from patients who performed evaluation of neck vessels for the presence of vascular risk factors at the Ultrasound Laboratory of the Neurologic Clinic of the Marche Polytechnic University Hospital after the exclusion of extra- and intra-cranial arteries plaque or stenosis through ultrasonographic examination.

Cerebral hemodynamics and cognitive functions were assessed at 6-month interval in both patients and controls. In patients undergoing CEA, the first assessment was performed before surgery.

Neurosonologic and neuropsychological evaluations were performed by trained operators blinded to the cognitive performance and hemodynamic status of the study's participants.

2.2 Cerebral hemodynamics assessment

Intracranial vessels were examined by means of a MultiDop X/TCD instrument (DWL Elektronische Systeme GmbH, Singen, Germany). Cerebral hemodynamics was assessed through the cerebral vasomotor reactivity (CVR) to hypercapnia as measured by the breath-holding index (BHI).⁶ Participants were requested to hold their breath for a period of 30 seconds, which was monitored by a capnometer. The BHI was obtained by dividing the percent increase in mean flow velocity (MFV) of middle cerebral artery occurring during breath-holding (BH) by the length of time (in seconds) that patients held their breath

after a normal inspiration ($[\text{MFV at the end of BH} - \text{rest MFV}] / \text{rest MFV} \times 100 / \text{seconds of BH}$).⁶ Three recordings were obtained at each side for any participant and their mean was considered.

2.3 Neuropsychological assessment

Coloured Progressive Matrices (CPM)⁷ plus Complex Figure Copy Test (CFCT),⁸ and the phonemic (ph) plus categorical (ca) Verbal Fluency (VF) tests⁹ were performed to assess right and left hemisphere functions, respectively. The selection of neuropsychological tests was based on prior studies demonstrating an asymmetry in cerebral function with increased activity of right-hemisphere during nonverbal, visual-spatial cognitive performances,^{10,11} and selective prevalence of left hemisphere during verbal tasks.^{12,13} All test scores were corrected for age and education according to normative data. Detailed description of all tests has been previously provided [I].

2.4 Statistical analysis

Values are presented as mean (SD) or median (interquartile range) for continuous variables and as the number (%) of patients for categorical variables. Univariate comparisons were made through the Student's t-test, one-way Analysis of Variance, or Chi-squared test, as appropriate. Tukey's honestly significant difference post hoc test was used. Changes in cognitive performance

were calculated by subtracting the baseline from 6-month follow-up values obtained in neuropsychological tests. In order to account for practice effect, Z scores for CEA patients were derived from the reference control group's performance, as follows: $Z \text{ score} = ([\text{change score}_{\text{CEA}} - \text{mean change score}_{\text{control}}] / \text{SD of change score}_{\text{control}})$. Change in CVR was the delta (δ) BHI obtained as the difference between postoperative and preoperative BHI values. A composite cognitive score was also estimated for any patient as the sum of the Z-scores from the two neuropsychological tests exploring the hemisphere ipsilateral to the ICA stenosis.

First, linear regression model was used by considering the Z score from any neuropsychological test as the dependent variable with δ BHI as predictor, and adjusting for age, sex, years of education, hypertension, and diabetes mellitus.¹⁴

Second, uni- and multivariate linear regression analyses were performed by considering the composite cognitive score as the dependent variable and the baseline characteristics of patients as the independent factors.

Results were considered significant for p values <0.05 (2 sided). Data analysis was performed using STATA/IC 13.1 statistical package (Stata-Corp LP, College Station, TX).

CHAPTER III

RESULTS

Hemodynamic and neuropsychological assessments before CEA were performed in 210 patients. Twenty-seven patients did not contribute any follow-up data and were excluded. Accordingly, 183 patients were included in the current analysis, whose 94 (51.4%) and 89 (48.6%) had right and left high-grade ICA stenosis, respectively. Some of the included patients contributed to previously published reports [I-II].

The mean age of the patients was 73.1 (6.9) years and 122 (66.7%) were males. Baseline characteristics of the patients are summarized in Table 1.

Before CEA, patients with right ICA performed worse on the CPM and CFCT and patients with left ICA stenosis performed worse on the (ph) and (ca) VF tests than either patients with contralateral ICA stenosis or controls. The BHI values on the side of ICA stenosis were lower than those observed on the contralateral side and in controls (Table 2).

The relationships between cerebral hemodynamics and cognitive performance at baseline are displayed in Figure 1.

Table 1. Baseline demographic and clinical characteristics

	Right ICA stenosis (n=94)	Left ICA stenosis (n=89)
Demographics		
Age (years)	73.2 (7.3)	73.0 (6.4)
Male sex	64 (68.1)	58 (65.2)
Education (years)	8.2 (3.8)	8.3 (4.1)
Clinical history		
Hypertension	57 (60.6)	54 (60.7)
Diabetes mellitus	18 (19.2)	22 (24.7)
Dyslipidaemia	36 (38.3)	31 (34.8)
Coronary artery disease	15 (16.0)	13 (14.6)
Current smoking	15 (16.0)	17 (19.1)
Medications		
Antihypertensives	64 (68.1)	59 (66.3)
Antidiabetics	18 (19.2)	20 (22.5)
Lipid lowering drugs	71 (75.5)	61 (68.5)
Antiplatelets	94 (100.0)	87 (97.8)

Data are mean (SD) for continuous variables, and n (%) for categorical variables.

*Adjusted $p < 0.05$ versus all other groups.

Abbreviation: ICA=internal carotid artery.

Table 2. Baseline neurocognitive functioning and cerebral hemodynamics

	Right ICA stenosis (n=94)	Left ICA stenosis (n=89)	Control Group (n=183)
Neurocognitive functioning			
Phonemic Verbal Fluency	20.0 (2.86)	12.9 (4.97)*	20.0 (1.98)
Category Verbal Fluency	21.7 (3.03)	14.6 (4.59)*	22.4 (1.90)
Coloured Progressive Matrices	26.6 (3.56)*	32.8 (2.66)	33.2 (1.54)
Complex Figure Copy Test	27.2 (3.68)*	33.2 (3.00)	33.8 (1.57)
Cerebral hemodynamics			
Ipsilateral BHI	0.55 (0.31)†	0.56 (0.32)†	1.08 (0.12)
Contralateral BHI	1.04 (0.20)	1.05 (0.19)	1.08 (0.13)

Data are mean (SD).

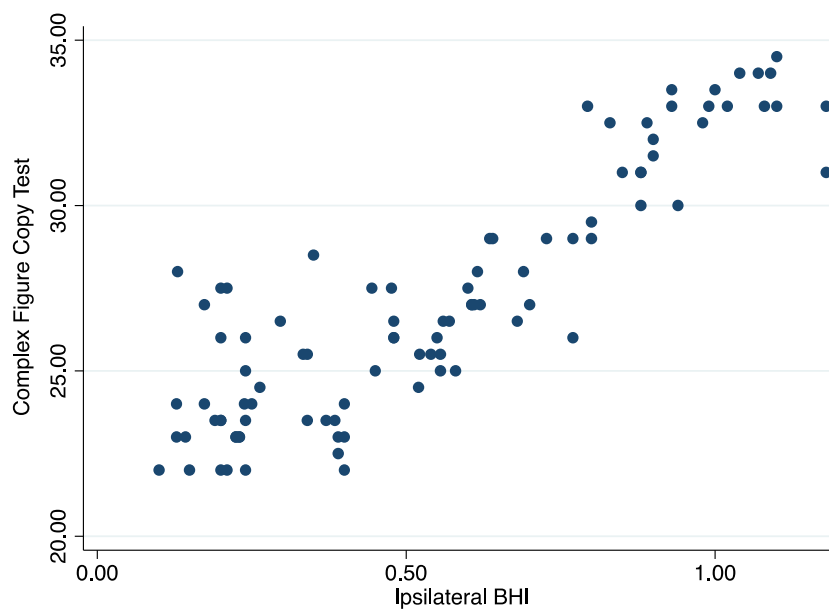
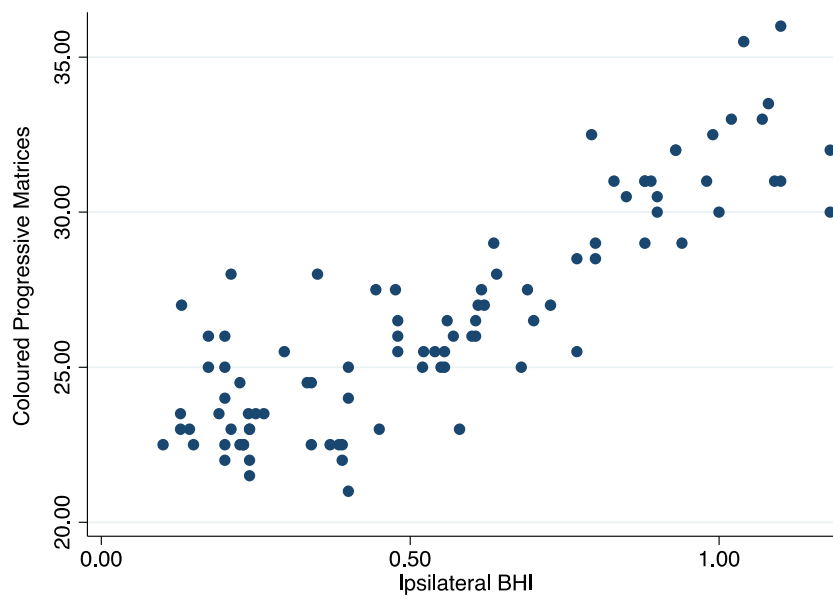
*Adjusted $p < 0.05$ versus all other groups.

†Adjusted $p < 0.05$ versus control group.

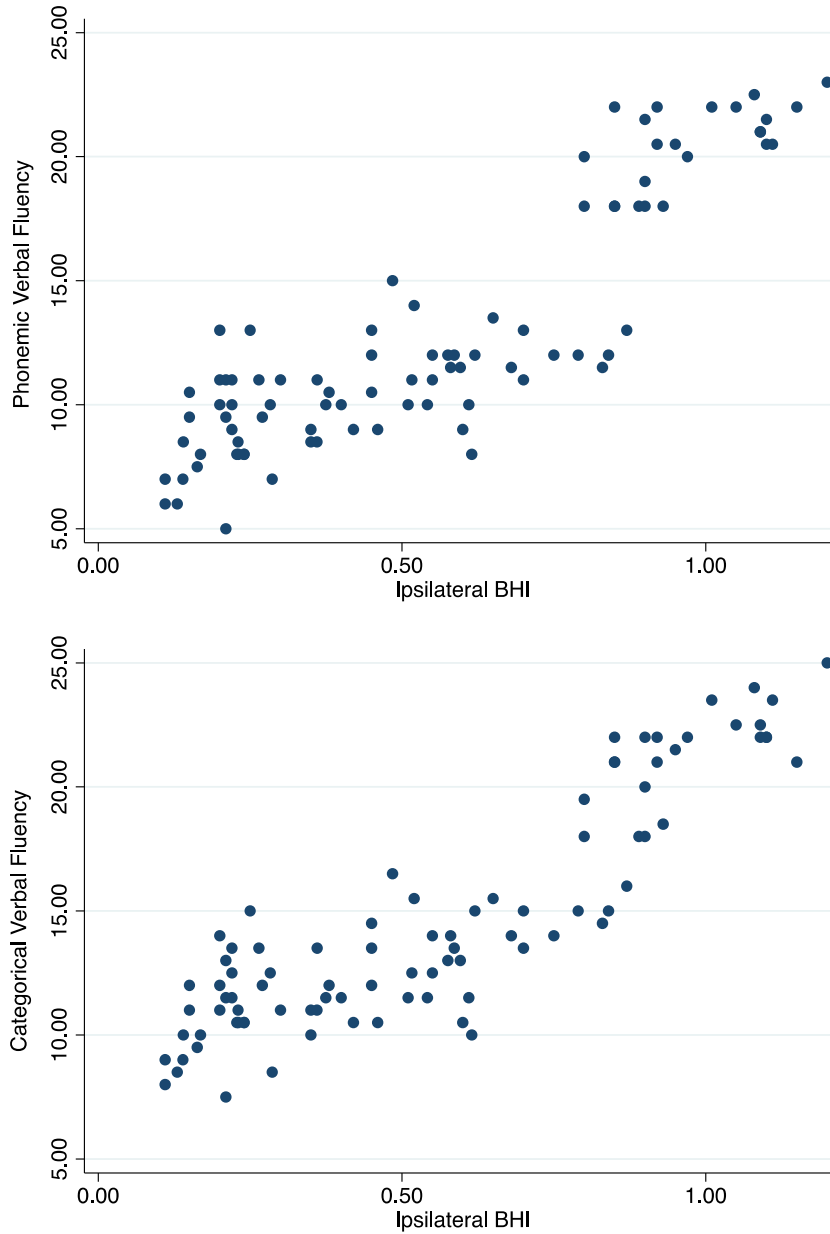
Abbreviations: BHI=breath-holding index, ICA=internal carotid artery.

Figure 1. Baseline cerebral hemodynamic and cognitive performance

A. Right internal carotid artery stenosis



B. Left internal carotid artery stenosis



Point to point graphs showing the relationship between BHI values on the side of carotid stenosis and scores in tests exploring cognitive functions of the ipsilateral hemisphere. Abbreviation: BHI=breath-holding index.

At the 6-month assessment, the CVR on the side of surgery and the scores obtained in neuropsychological tests evaluating the functions of the revascularized hemisphere were significantly improved in both patient groups (Table 3). No meaningful changes were observed in cerebral hemodynamics or cognitive performance in controls.

In patients who underwent right CEA, the mean Z-score was 1.54 (1.37) for the CPM and 1.73 (1.64) for the CFCT. In patients who performed left CEA, the mean Z-score resulted 1.61 (1.43) and 1.46 (1.35) for the tests evaluating (ph) and (ca)VF.

The relationships between the changes observed in CVR and neurocognitive functioning after CEA according to the side of carotid stenosis are shown in Figure 2.

Table 3. Neuropsychological performance and cerebral hemodynamics before and after carotid endarterectomy

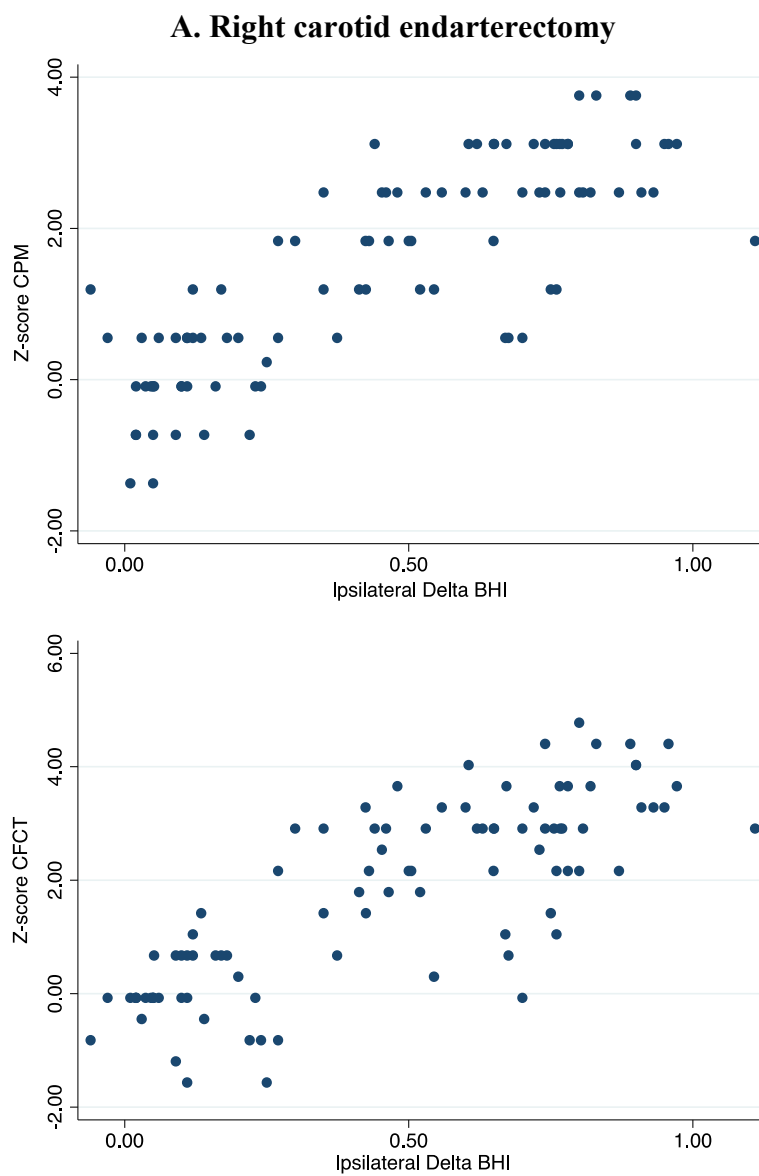
	Before CEA	After CEA	p value*
Right ICA stenosis			
Phonemic Verbal Fluency	20.0 (2.86)	20.3 (2.76)	0.130
Category Verbal Fluency	21.7 (3.03)	22.0 (2.66)	0.141
Coloured Progressive Matrices	26.6 (3.56)	29.1 (2.85)	<0.001
Complex Figure Copy Test	27.2 (3.68)	29.6 (2.80)	<0.001
Ipsilateral BHI	0.55 (0.31)	1.00 (0.21)	<0.001
Contralateral BHI	1.04 (0.20)	1.07 (0.12)	0.070
Left ICA stenosis			
Phonemic Verbal Fluency	12.9 (4.97)	16.6 (3.99)	<0.001
Category Verbal Fluency	14.6 (4.59)	18.2 (3.98)	<0.001
Coloured Progressive Matrices	32.8 (2.66)	33.1 (2.09)	0.197
Complex Figure Copy Test	33.2 (3.00)	33.4 (2.12)	0.119
Ipsilateral BHI	0.56 (0.32)	1.00 (0.19)	<0.001
Contralateral BHI	1.05 (0.19)	1.05 (0.12)	0.601

Data are mean (SD).

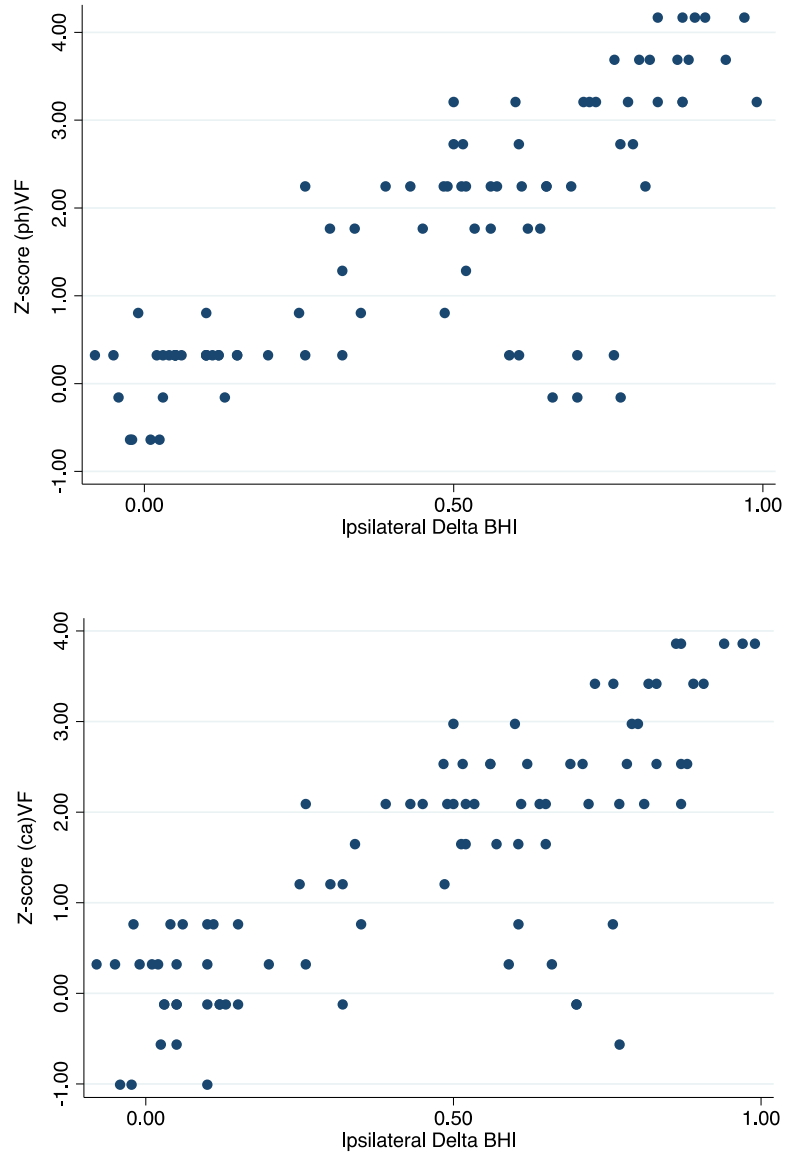
*Paired t test.

Abbreviations: BHI=breath-holding index, CEA=carotid endarterectomy, ICA=internal carotid artery.

Figure 2. Cerebral hemodynamic and cognitive changes after surgical stenosis correction



B. Left carotid endarterectomy



Change in CVR was the difference between post- and pre-surgery BHI values. Change in each neuropsychological test was expressed by means of Z-score derived from control group's performance change. Abbreviations: BHI=breath-holding index, (ca)VF=categorical verbal fluency, CEA=carotid endarterectomy, CFCT=Complex Figure Copy Test, CPM=Coloured Progressive Matrices, CVR=cerebral vasomotor reactivity, (ph)VF=phonemic verbal fluency.

According to multiple regression analysis, the change observed after stenosis correction in tests exploring the cognitive functions of the revascularized hemisphere was positively associated with ipsilateral δ BHI, being the increase in CVR related to improved neuropsychological performance (Table 4).

Table 4. Associations between cognitive and hemodynamic changes after carotid endarterectomy

Dependent Variable	Ipsilateral δ BHI					
	Unadjusted			Adjusted*		
	β	95% CI	p	β	95% CI	p
Right ICA stenosis						
CPM	3.60	3.06-4.09	<0.001	3.52	3.02-4.03	<0.001
CFCT	4.16	3.51-4.81	<0.001	4.10	3.43-4.76	<0.001
Left ICA stenosis						
(ph)VF	3.60	3.02-4.18	<0.001	3.62	3.06-4.17	<0.001
(ca)VF	3.33	2.77-3.89	<0.001	3.39	2.85-3.93	<0.001

Values are from linear regression model with Z-score of change in neuropsychological test performance as dependent variable.

*Adjustment for age, sex, education years, hypertension and diabetes mellitus.

Abbreviations: BHI=breath-holding index, CI=confidence interval, (ca)VF=categorical verbal fluency, CFCT=Complex Figure Copy Test, CPM=Coloured Progressive Matrices, ICA=internal carotid artery, (ph)VF=phonemic verbal fluency.

The mean composite cognitive change scores were 3.26 (2.94) and 3.07 (2.73) ($p=0.645$) in patients who underwent right and left ICA stenosis correction, respectively. Linear regression analyses were modelled to identify the baseline predictors of the post-operative cognitive outcome (Table 5).

According to the multivariable model, the 6-month performance change in the neuropsychological tests exploring the re-vascularized hemisphere was inversely associated with age [$\beta=-0.17$, 95% confidence interval (CI) -0.22 to -0.11; $p<0.001$] and pre-operative ipsilateral BHI ($\beta=-6.30$, 95% CI -7.44 to -5.15; $p<0.001$).

Scatterplots of the relationships between cerebral hemodynamics at baseline and cognitive performance change after CEA according to the side of carotid stenosis are shown in Figure 3.

Table 5. Associations of baseline characteristics with neuropsychological performance change at 6 months from carotid endarterectomy

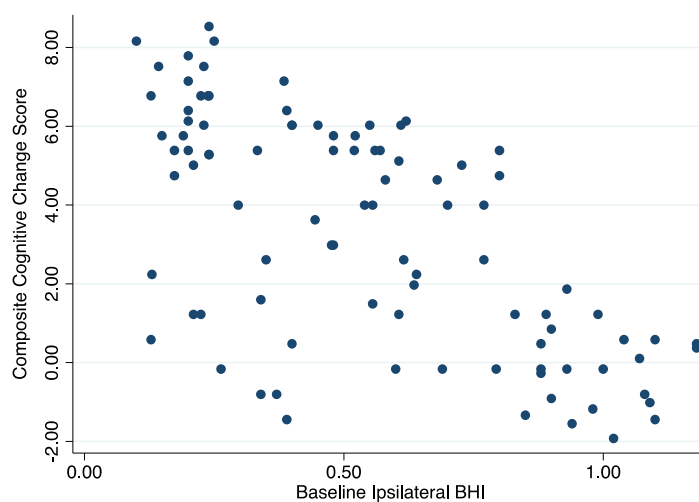
Dependent Variable	Univariate			Multivariable*		
	β	95% CI	p value	β	95% CI	p value
Age	-0.11	-0.17 to -0.05	<0.001	-0.17	-0.22 to -0.11	<0.001
Sex	-0.06	-0.94 to 0.82	0.892	-0.25	-0.93 to 0.43	0.469
Side of stenosis	0.19	-0.64 to 1.02	0.645	0.18	-0.43 to 0.78	0.565
Education	0.15	0.04 to 0.25	0.006	-0.01	-0.10 to 0.07	0.763
Smoking	0.17	-0.92 to 1.27	0.753	-0.13	-1.00 to 0.74	0.768
Hypertension	0.64	-0.20 to 1.48	0.137	-0.55	-1.96 to 0.87	0.447
Diabetes mellitus	0.12	-0.88 to 1.13	0.811	0.90	-2.01 to 3.81	0.543
Dyslipidaemia	0.05	-0.81 to 0.91	0.916	-0.33	-1.07 to 0.42	0.387
CHD	-0.93	-2.08 to 0.21	0.109	-0.88	-1.91 to 0.15	0.092
Antihypertensives	0.64	-0.23 to 1.52	0.150	0.93	-0.62 to 2.48	0.239
Antidiabetics	0.08	-0.94 to 1.10	0.877	-1.51	-4.48 to 1.47	0.319
Lipid lowering drugs	0.13	-0.79 to 1.05	0.781	-0.05	-0.85 to 0.75	0.900
Antiplatelets	0.71	-3.28 to 4.70	0.726	0.63	-2.35 to 3.60	0.678
Ipsilateral BHI	-5.44	-6.51 to -4.38	<0.001	-6.30	-7.44 to -5.15	<0.001
Contralateral BHI	-3.79	-5.85 to -1.74	<0.001	0.85	-0.91 to 2.61	0.341

Values are from linear regression model with composite cognitive change scores as dependent variable.

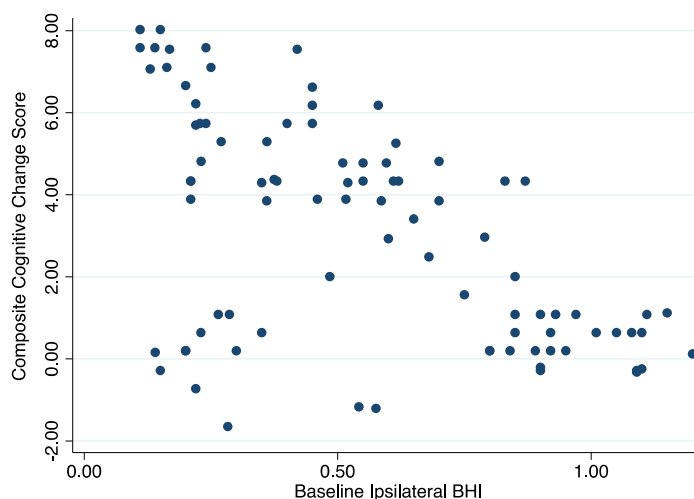
*Fully adjusted model including all the variables considered in the univariate analysis. Abbreviations: BHI=breath-holding index, CHD=coronary artery disease, CI=confidence interval, ICA=internal carotid artery.

Figure 3. Cognitive performance change after carotid endarterectomy and pre-operative cerebral hemodynamics

A. Right carotid endarterectomy



B. Left carotid endarterectomy



Point to point graph shows the relationship between composite cognitive performance change at 6 months after surgical stenosis correction and pre-operative cerebral hemodynamics on the side of revascularization. Composite cognitive change score was obtained for each patient as the sum of the Z-scores from the neuropsychological tests exploring the revascularized hemisphere. Abbreviation: BHI=breath-holding index.

CHAPTER IV

DISCUSSION

The main findings of the current study were the relationship between the cerebral hemodynamic status and cognitive performance in patients with symptomatic unilateral high-grade ICA stenosis and the association between the increase in cerebral vasomotor response and improvement in neurocognitive functioning following surgical correction of carotid stenosis.

Patients with severe ICA stenosis and history of TIA showed decreased CVR on the side of the carotid narrowing and reduced scores on the tests exploring the cognitive domains of the ipsilateral hemisphere.

The cognitive performance improved after surgical stenosis correction and the improvement was independently associated with the increase in cerebral vasomotor response on the side of revascularization. In addition, the patients whose cerebral hemodynamics was more compromised at baseline were those who presented the greater enhancement in neurocognitive functioning following CEA.

These findings build up the notion that cerebrovascular hemodynamic insufficiency can act as one pathogenic mechanism underpinning the cognitive impairment associated with the atherosclerotic disease of the carotid artery.¹⁴⁻¹⁶

In this regard, cerebrovascular reactivity can synthesize the degree of the

compensatory dilation of cerebral arterioles that occurs to preserve blood flow distally to a carotid stenosis, and represent a reliable index of cerebral hemodynamic status.^{17,18} Remarkably, the reduction of BHI values on the side of ICA stenosis can reflect the degree of impairment of cerebral vasomotor reserve and identify a condition of cerebral hypo-perfusion that may be responsible for the reduction in cognitive abilities involving the function of ipsilateral brain areas.¹⁹

Surgical revascularization can enhance cerebral perfusion and restore brain autoregulation. The increase in CVR following stenosis correction can, hence, translate into the improvement of cognitive abilities that were detrimentally affected on a hemodynamic basis for the effects of the carotid stenosis. The hypothesis of reversible cognitive dysfunction is further supported by the evidence that the benefit in neurocognitive functioning was obtained at a greater extent by those patients who had a greater impairment of CVR at baseline and achieved a more pronounced enhancement in cerebral vasomotor response after CEA.

The current results can also contribute to explain the conflicting results coming from the studies that, so far, have explored the changes in cerebral hemodynamics and cognitive outcome in patients with ICA stenosis undergoing surgical stenosis correction.³ Indeed, patients with different hemodynamic status

have been enrolled and variations in cognitive tests have not been assessed according to changes occurring in brain perfusion and vasomotor reactivity after revascularization.

Some shortcomings need to be taken into account when interpreting the current findings, like the observational, single-center, non-randomized and placebo-uncontrolled nature of the study. In addition, data about brain atrophy and burden of white matter lesions have not been systematically collected and their contribute to the cognitive status and hemodynamic changes have not been addressed.

The key strenghts of the study included the prospective design and the sound methodology, including the estimate of Z scores and the domain-specific assessement of cognitive performance.

The reference to a control group and the 6-month time frame between the evaluations allowed to minimize the learning and practical effects and provide a reliable mesure of the hemodynamic and cognitive changes observed in patients due to carotid revascularization.^{20,21} The selective inclusion of patients with history of TIA avoided the potential confounding effects of acute cerebral damage and post-stroke plasticity.

4.1 Conclusion

Cerebral hemodynamics can contribute to cognitive impairment in patients with symptomatic high-grade ICA stenosis and CEA can be associated with significant improvement in neurocognitive functioning by the enhancement of cerebral blood flow and hemodynamic reserve.

Carotid stenosis correction may offer more than the prophylaxis of acute cerebral ischemic events and result into cognitive improvement in patients whose neuropsychological performance is negatively affected by the reduction in cerebral vasoreactivity.

Further investigations are warranted to investigate whether these findings can be extended to patients with ICA stenosis and no history of cerebral and/or ocular ischemic events referable to the carotid stenosis itself. This would allow to refine the definition of “asymptomatic” carotid artery disease and criteria for surgical revascularization, and pre-operatively identify the patients with the greater likelihood to gain a benefit in their cognitive performance.

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