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Clinical Short Communication

Predictors of cognitive functioning after carotid revascularization

Simona Lattanzi[a,*], Luciano Carbonari[b], Gabriele Pagliariccio[b], Claudia Cagnetti[a], Simona Luzzi[a], Marco Bartolini[a], Laura Buratti[a], Leandro Provinciali[a], Mauro Silvestrini[a]

[a] Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy
[b] Vascular Surgery, Ospedali Riuniti of Ancona, Ancona, Italy

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ABSTRACT

Purpose: High-grade carotid stenosis can affect cognition, but the relationship between stenosis correction and cognitive outcome is not fully understood, yet. The aim of this study was to evaluate the predictors of post-operative neurocognitive functioning in patients with symptomatic severe internal carotid artery (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 hemodynamics was assessed by means of the cerebral vasomotor reactivity (CVR) to hypercapnia measured through transcranial Doppler ultrasonography. Coloured Progressive Matrices plus Complex Figure Copy Test, and phonemic plus categorical (ca) Verbal Fluency tests were performed to assess right and left hemisphere cognitive functions, respectively. Cerebral hemodynamics and cognitive functions were assessed before and 6 months after CEA.

Results: One hundred and eighty-one patients were included. The mean age was 73.2 (6.9) years and 121 (66.9%) were males. At 6 months from CEA, the scores obtained in the cognitive tests exploring the re-vascularized hemisphere's functions and ipsilateral cerebral hemodynamics were improved. At multivariate linear regression analysis, the 6-month change in cognitive performance was inversely associated with age [ß = −0.17, 95% confidence interval (CI) −0.22 to −0.12; $p < .001$] and CVR value obtained before CEA on the side of ICA stenosis (ß = −6.25, 95% CI −7.40 to −5.10; $p < .001$).

Conclusions: In patients with symptomatic high-grade ICA stenosis, age and cerebral hemodynamic status before CEA predicted the neurocognitive performance changes after surgical stenosis correction.

1. Introduction

Atherosclerotic carotid disease can cause transient ischemic attack (TIA) and ischemic stroke, and carotid endarterectomy (CEA) is currently recommended as secondary prevention of brain ischemia in patients with symptomatic stenosis of the internal carotid artery (ICA) [1,2]. Although there is evidence that high-grade carotid stenosis can also affect cognition, the relationship between stenosis correction and cognitive outcome is not yet fully understood [3]. Recently, we have shown that patients with high-grade ICA stenosis undergoing CEA had decreased cerebrovascular reactivity on the stenotic side and reduced scores on the tests exploring the neuropsychological functions of the ipsilateral hemisphere [4]. The neurocognitive performance improved after carotid revascularization, and cognitive changes correlated with the enhancement of cerebral hemodynamics [4].

In this study, we aimed to explore the associations between baseline individual characteristics and change in neurocognitive functioning in patients with high-grade symptomatic ICA stenosis at 6 months from CEA in order to identify potential predictors of cognitive outcome.

2. Materials and methods

2.1. Study subjects

Participants were patients who underwent CEA at the Vascular Surgery of the Ospedali Riuniti of Ancona (Ancona, Italy) from January 2014 to December 2016 and had suffered transient ischemic attack within the past 6 months due to an ipsilateral severe (70%–99%) ICA stenosis, as documented by non-invasive imaging (computed tomography angiogram or magnetic resonance angiogram) [5]. Stenosis degree was estimated according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [6]. All patients

* Corresponding author at: Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Via Conca 71, 60020 Ancona, Italy.
E-mail address: alfierelattanzisimona@gmail.com (S. Lattanzi).

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underwent complete blood work, clinical history, neurologic examination, brain magnetic resonance, electrocardiography and transthoracic echocardiography. Exclusion criteria were: carotid occlusion, vertebrobasilar or intracranial steno-occlusive disease, contralateral ICA stenosis ≥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/non-compliance with the cerebrovascular reactivity assessment with transcranial Doppler ultrasonography, left-handedness as by the Edinburgh Handedness Inventory [7]. Controls were age- and sex-matched subjects performing evaluation of neck vessels for the presence of vascular risk factors at the Ultrasound Laboratory of the Neurological Clinic of the Marche Polytechnic University Hospital after the exclusion of extra- and intra-cranial arteries plaque or stenosis trough ultrasonographic exam.

Cerebral hemodynamics and cognitive functions were assessed at 6-month interval; the first evaluation preceded CEA. Trained operators performed neurosonologic and neuropsychological evaluations blinded to subjects' cognitive performance and hemodynamic status, respectively.

2.2. Cerebral hemodynamics assessment

Intracranial vessels were examined by means of a MultiDop X/TCD instrument (DWL Elektronische Systeme GmbH, Singen, Germany). Cerebral hemodynamic was assessed through the cerebral vasomotor reactivity (CVR) to hypercapnia as measured by the breath-holding index (BHI) [8]. 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 subjects held their breath after a normal inspiration [(MFV at the end of BH - rest MFV)/rest MFV x 100/s of BH] [8]. For each subject, three recordings were obtained at each side and their mean was considered.

2.3. Neuropsychological assessment

The Coloured Progressive Matrices (CPM) [9] plus Complex Figure Copy Test (CFCT) [10], and the phonemic (ph) plus categorical (ca) Verbal Fluency (VF) tests [11] 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 non-verbal, visual-spatial cognitive performances [12,13], and selective prevalence of left hemisphere during verbal tasks [14,15]. All test scores were corrected for age and education according to normative data; detailed description has been reported elsewhere [4].

2.4. Statistical analysis

Values are presented as mean (SD) for continuous variables and as the number (percent) of subjects for categorical variables. Univariate comparisons were made through the Student *t*-test or Chi-squared test, as appropriate. Changes in cognitive performance were calculated by subtracting the baseline from 6-month 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-score = [(change score $_{CEA}$ - mean change score $_{control}$)/SD of change score $_{control}$]. Control subjects represented the reference to derive Z-scores and were not included in any other analysis or reported otherwise in the present study. A composite cognitive score was obtained for each patient as the sum of the *Z*-scores from the two neuropsychological tests exploring the hemisphere ipsilateral to the ICA stenosis. Uni- and multivariate linear regression analysis was performed by considering the composite cognitive score as the dependent variable and the baseline characteristics of patients as the independent factors. Spearman correlation was used to correlate continuous variables. Results were considered significant for p values < 05 (two sided). Data analysis was performed using STATA/IC 13.1 statistical package (StataCorp LP, Texas, USA).

2.5. Standard protocol approvals, registrations, and patient consents

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

2.6. Data availability

Anonymized data will be shared by request from any qualified investigator.

3. Results

A total of 208 patients underwent hemodynamic and neuropsychological assessment before CEA, of which 27 did not contribute any follow-up data and were excluded. Accordingly, a total of 181 patients were included in the current analysis, whose 93 (51.0%) and 88 (49.0%) presented with right and left severe ICA stenosis, respectively. One hundred and thirty-seven out of 181 patients contributed to a previously published report [4]. The mean age of the study cohort was 73.2 (6.9) years and 121 (66.9%) were males. The demographic and clinical characteristics of the patients at baseline are summarized in Table 1. The time window between the index event and CEA was 9 (3–15) days, and neuropsychological and TCD evaluations were performed 1–3 days before surgery. Perioperative complications occurred in 11 (6.1%) of the included patients (myocardial infarction $n = 1$, minor stroke $n = 1$, TIA $n = 4$, cranial nerve palsy $n = 3$, neck hematoma $n = 2$).

At the 6-month evaluation, the mean BHI values recorded on the side of surgery were 1.00 (0.21) and 1.01 (0.19) in patients undergoing right and left CEA, and they were significantly higher in comparison to the corresponding baseline values ($p < .001$). The mean difference between post- and pre-operative BHI values on the stenotic side was

Table 1
Baseline characteristics of patients.

	Left ICA stenosis (n = 88)	Right ICA stenosis (n = 93)	p value
Demographics			
Age (years)	73.1 (6.4)	73.2 (7.3)	0.921[a]
Male sex	58 (65.9)	63 (67.7)	0.793[b]
Education (years)	8.3 (4.1)	8.2 (3.8)	0.862[a]
Clinical history			
Current smoking	16 (18.2)	15 (16.1)	0.714[b]
Hypertension	54 (61.4)	56 (60.2)	0.874[b]
Diabetes mellitus	21 (23.9)	18 (19.4)	0.461[b]
Dyslipidaemia	30 (34.1)	36 (38.7)	0.519[b]
Coronary artery disease	13 (14.8)	15 (16.1)	0.801[b]
Medications			
Antihypertensives	59 (67.1)	63 (67.7)	0.920[b]
Antidiabetics	19 (21.6)	18 (19.4)	0.709[b]
Lipid lowering drugs	60 (68.2)	70 (75.3)	0.289[b]
Antiplatelets	86 (97.7)	93 (100.0)	0.144[b]
Cerebral hemodynamics			
Ipsilateral BHI	0.55 (0.32)	0.55 (0.31)	0.921[a]
Contralateral BHI	1.05 (0.19)	1.04 (0.21)	0.851[a]

Data are mean (SD) for continuous variables, and n (%) for categorical variables.
Abbreviations: BHI = breath-holding index, ICA = internal carotid artery.
[a] Two-sample *t*-test.
[b] Chi-squared test.

Table 2
Neuropsychological performance before and after carotid endarterectomy.

	Before CEA	After CEA	*p* value*
Left ICA stenosis			
Phonemic verbal fluency	12.9 (4.97)	16.6 (4.00)	< **0.001**
Category verbal fluency	14.6 (4.61)	18.2 (4.01)	< **0.001**
Coloured progressive matrices	32.8 (2.66)	33.1 (2.10)	0.177
Complex figure copy test	33.2 (3.02)	33.4 (2.13)	0.128
Right ICA stenosis			
Phonemic verbal fluency	19.9 (2.87)	20.3 (2.77)	0.130
Category verbal fluency	21.7 (3.05)	22.0 (2.66)	0.155
Coloured progressive matrices	26.5 (3.55)	29.1 (2.85)	< **0.001**
Complex figure copy test	27.1 (3.66)	29.5 (2.79)	< **0.001**

Abbreviations: CEA = carotid endarterectomy, ICA = internal carotid artery. Bold signifies $p < 0.05$
* Paired *t*-test.

0.46 (0.32) in the study cohort. The mean BHI obtained on the side contralateral to the ICA stenosis was 1.07 (0.12) in patients undergoing right CEA and 1.05 (0.12) in patients undergoing left CEA; there were no significant differences between pre- and post-operative CVR values on the side contralateral to the intervention (right CEA: $p = .065$; left CEA: $p = .607$).

The scores obtained in the neuropsychological tests before CEA and after 6 months are reported in Table 2. The performance in the tests exploring the functions of the re-vascularized hemisphere was significantly improved in both the patient groups. In patients undergoing right CEA, the mean *Z*-score was 1.55 (1.38) for the CPM and 1.74 (1.64) for the CFCT. In patients undergoing left CEA, the mean Z-score resulted 1.63 (1.43) and 1.47 (1.34) for the tests evaluating (ph) and (ca)VF. The mean composite cognitive change scores were 3.29 (2.95) and 3.10 (2.73) ($p = .665$) in patients who underwent right and left ICA stenosis correction, respectively.

The results of linear regression analysis exploring the associations between the composite cognitive change score and baseline characteristics of patients are synthetized in Table 3. According to the multivariable model, the 6-month performance change in the cognitive tests exploring the re-vascularized hemisphere was inversely associated with age [ß = −0.17, 95% confidence interval (CI) −0.22 to −0.12; $p < .001$] and pre-operative ipsilateral BHI (ß = −6.25, 95% CI −7.40 to −5.10; $p < .001$).

The 6-month composite cognitive performance changes according to pre-operative ipsilateral BHI values are shown in Fig. 1. The

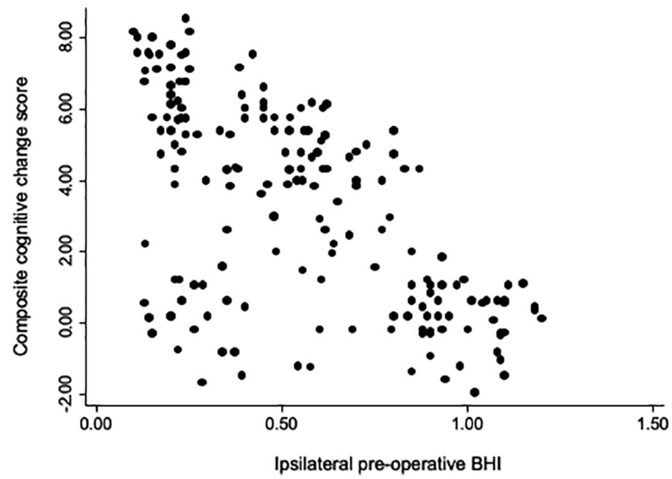

Fig. 1. Cognitive performance change following carotid endarterectomy and pre-operative cerebral hemodynamics.
Point to point graph shows the relationship between composite cognitive performance change observed 6 months after CEA and pre-operative cerebral vasomotor reactivity on the side of revascularization. Composite cognitive change score was obtained for each patient as the sum of the *Z*-scores from the two neuropsychological tests exploring the hemisphere ipsilateral to the ICA stenosis. Z-scores for CEA patients were derived from the reference control group's performance, as follows: Z-score = [(change score $_{CEA}$ − mean change score $_{control}$)/SD of change score $_{control}$].
Abbreviations: BHI = breath-holding index; CEA = carotid endarterectomy; ICA = internal carotid artery; SD = standard deviation.

Spearman correlation analysis revealed a strong inverse correlation between baseline BHI on the stenotic side and ipsilateral change in CVR, estimated as the difference between post- and pre-surgery BHI values (Spearman rho = −0.777, $p < .001$), and a weak correlation between age and baseline BHI on the side of ICA stenosis (Spearman rho = −0.169, $p = .023$).

4. Discussion

One main finding of this study was the independent association between pre-operative cerebral hemodynamics with changes in cognitive performance observed 6 months after CEA in patients with high-grade symptomatic ICA stenosis. Indeed, the patients whose CVR

Table 3
Associations of baseline characteristics with neuropsychological performance change at 6 months from carotid endarterectomy.

Dependent variable	Univariate			Multivariable*		
	β coefficient	95% CI	*p* value	β coefficient	95% CI	*p* value
Age	−0.11	−0.17 to −0.05	< 0.001	−0.17	−0.22 to −0.12	< **0.001**
Sex	−0.03	−0.91 to 0.86	0.951	−0.24	−0.93 to 0.45	0.488
Side of ICA stenosis	0.18	−0.65 to 1.02	0.665	0.18	−0.44 to 0.79	0.57
Education	0.14	0.04 to 0.25	0.007	−0.02	−0.11 to 0.07	0.699
Current smoking	0.26	−0.85 to 1.37	0.641	−0.11	−0.99 to 0.77	0.805
Hypertension	0.62	−0.23 to 1.47	0.15	−0.54	−1.95 to 0.88	0.455
Diabetes mellitus	0.19	−0.83 to 1.20	0.716	0.89	−2.03 to 3.82	0.546
Dyslipidaemia	0.07	−0.79 to 0.94	0.865	−0.33	−1.08 to 0.43	0.391
Coronary artery disease	−0.97	−2.11 to 0.18	0.098	−0.91	−1.95 to 0.13	0.085
Antihypertensives	0.62	−0.27 to 1.50	0.17	0.91	−0.65 to 2.47	0.251
Antidiabetics	0.15	−0.89 to 1.18	0.777	−1.48	−4.46 to 1.51	0.329
Lipid lowering drugs	0.17	−0.76 to 1.10	0.72	−0.01	−0.82 to 0.79	0.976
Antiplatelets	0.74	−3.25 to 4.73	0.716	0.64	−2.34 to 3.63	0.67
Ipsilateral BHI	−5.41	−6.49 to −4.34	< 0.001	−6.25	−7.40 to −5.10	< **0.001**
Contralateral BHI	−3.78	−5.85 to −1.72	< 0.001	0.83	−0.93 to 2.60	0.353

Values are from linear regression model with composite cognitive change scores as dependent variable (see text for details). Bold signifies $p < 0.05$
Abbreviations: BHI = breath-holding index, CI = confidence interval, ICA = internal carotid artery.
* Fully adjusted model including all the variables considered in the univariate analysis.

ipsilateral to the stenosis was more compromised before CEA had the greater improvement in their performance on the neuropsychological tests exploring the revascularized hemisphere following surgery.

These data add evidence to the notion that hemodynamic insufficiency can be one pathogenic, potentially reversible, mechanism underlying cognitive dysfunction in patients with carotid artery disease [3]. Animal models revealed that cognition is detrimentally affected by chronic cerebral hypoperfusion due to carotid occlusive disease and this state reversed with restoration of blood flow [16]. In clinical studies, hemodynamic impairment in high-grade ICA stenosis has been associated with lower cognitive performances and increased risk to develop cognitive deterioration in comparison to either healthy controls or patients with carotid stenosis and preserved cerebral hemodynamics [17–19]. In this regard, the cerebral vasomotor response can provide reliable information about the status of compensatory dilation of intracranial arterioles that occurs distally to a carotid narrowing to counteract the drop in brain perfusion [20,21]. Signally, the decrease in CVR to hypercapnia ipsilateral to the ICA stenosis can reflect the impairment of the hemodynamic reserve [20], and indicate a condition of tissue hypo-perfusion, which may contribute to the impairment in cognitive abilities involving the activation of areas of the ipsilateral hemisphere [3]. Anatomical changes induced by reduced blood flow may also play role in cognitive dysfunction: altered cerebral hemodynamics has been associated with cortical thinning on the side of ICA stenosis [22], and surgical revascularization was followed by restoration of thickness [23].

Age was also an independent predictor of cognitive performance changes after CEA and was inversely related with the improvement obtained in the neuro-psychological tests administered after surgery. Different hypotheses may be advanced to explain this relationship. Older age may be associated with a higher burden of structural brain abnormalities, like silent ischemic infarcts and white matter lesions, which may act as determinants of cognitive dysfunction and are not amenable to reverse through revascularization [24,25]. In addition, structural, mechanical and functional changes of vasculature that occur with aging may hamper, reduce or delay the beneficial effects of blood flow restoration on cerebrovascular reactivity [26,27].

The current findings can also provide cues to interpret the still controversial evidence about the effects of stenosis correction on cognitive functions. Indeed, the heterogeneity of patients in their baseline characteristics and the lack of data analysis according to the hemodynamic impact of ICA stenosis could contribute to explain the disagreement between studies yielding contradictory results [28].

This study inherited the obvious limits associated with the placebo-uncontrolled design. Further, the lack of a systematic collection of data about brain atrophy, white matter lesions and micro-embolic infarcts prevented to investigate the contributory role of brain structural abnormalities to the neurocognitive performances and their interactions with cerebral hemodynamics in determining the post-surgery outcome. Major strengths included the prospective nature of the study, the blindness of the investigators performing the assessments, the sound statistical approach, including the reference to a control-group and the estimate of domain-specific *Z*-scores as reliable change indices, and the 6-month interval between the neuropsychological testing to minimize the learning effect [29]. Finally, although the selective inclusion criteria limited the generalizability of the findings to patients with unilateral high-grade ICA stenosis and history of TIA, they allowed to avoid the potential confounding effects of post-stroke recovery or plasticity and explore the changes primarily induced by revascularization.

5. Conclusion

Cerebral hemodynamics is suggested to contribute to cognitive dysfunction in patients with severe carotid artery disease and CEA may result in the improvement in cognitive performance. The study added useful insights toward the opportunity to pre-operatively select a subset of patients with the higher likelihood to gain a benefit from the stenosis correction on the basis of hemodynamic parameters. Additional research should be directed to evaluate whether threshold values in baseline hemodynamics or cognitive performance could increase the accuracy of outcome prediction. Furthermore, it would be really interesting to explore whether these findings are significant in patients presenting with "asymptomatic" carotid disease and decreased cognitive performance: this would allow advancing in the understanding of the pathophysiology of vascular cognitive impairment and refining the definition of symptomatic status and selection criteria for revascularization of ICA stenosis.

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Declaration of Competing Interest

All Authors report no disclosures.

References

[1] W.N. Kernan, B. Ovbiagele, H.R. Black, D.M. Bravata, M.I. Chimowitz, M.D. Ezekowitz, et al., American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease, Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 45 (2014) 2160–2236.

[2] A.L. Abbott, K.I. Paraskevas, S.K. Kakkos, J. Golledge, H.H. Eckstein, L.J. Diaz-Sandoval, et al., Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis, Stroke 46 (2015) 3288–3301.

[3] C. Balucani, M. Silvestrini, Carotid atherosclerotic disease and cognitive function: mechanisms identifying new therapeutic targets, Int. J. Stroke 6 (2011) 368–369.

[4] S. Lattanzi, L. Carbonari, G. Pagliariccio, et al., Neurocognitive functioning and cerebrovascular reactivity after carotid endarterectomy, Neurology. 90 (2018) e307–e315.

[5] J.D. Easton, J.L. Saver, G.W. Albers, M.J. Alberts, S. Chaturvedi, E. Feldmann, et al., Definition and evaluation of transient ischemic attack. A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association stroke council; council on cardiovascular surgery and anesthesia; council on cardiovascular radiology and intervention; council on cardiovascular nursing; and the interdisciplinary council on peripheral vascular disease, Stroke 40 (2009) 2276–2293.

[6] North American Symptomatic Carotid Endarterectomy Trial Collaborators, Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis, N. Engl. J. Med. 325 (1991) 445–453.

[7] R.C. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, Neuropsychologia 9 (1971) 97–113.

[8] H.S. Markus, M.J. Harrison, Estimation of cerebrovascular reactivity using transcranial Doppler, including the use of breath-holding as the vasodilatory stimulus, Stroke 23 (1992) 668–673.

[9] J.C. Raven, Mental Tests Used in Genetic Studies: The Performance of Related Individuals on Tests Mainly Educative and Mainly Reproductive [MSc Thesis], University of London, London, 1936.

[10] P.A. Osterrieth, Le test de copie d'une figure complexe: contribution a l'e'tude de la perception et de la memoire, Arch. Psychol. 30 (1944) 286–350.

[11] M.D. Lezak, D.B. Howieson, E.D. Bigler, D.T. Lezak, Neuropsychological Assessment, Oxford University Press, New York, 1995.

[12] S. Kastner, M.A. Pinsk, P. De Weerd, R. Desimone, L.G. Ungerleider, Increased activity in human visual cortex during directed attention in the absence of visual stimulation, Neuron 22 (1999) 751–761.

[13] M. Corbetta, M.J. Kincade, C. Lewis, A.Z. Snyder, A. Sapir, Neural basis and recovery of spatial attention deficits in spatial neglect, Nat. Neurosci. 8 (2005) 1603–1610.

[14] J.R. Binder, S.M. Rao, T.A. Hammeke, J.A. Frost, P.A. Bandettini, A. Jesmanowicz, et al., Lateralized human brain language systems demonstrated by task subtraction functional magnetic resonance imaging, Arch. Neurol. 52 (1995) 593–601.

[15] N. Stroobant, G. Vingerhoets, Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: a review, Neuropsychol. Rev. 10 (2000) 213–231.

[16] J.C. de la Torre, T. Fortin, G.A. Park, B.A. Pappas, M.T. Richard, Brain blood flow restoration 'rescues' chronically damaged rat CA1 neurons, Brain Res. 623 (1993) 6–15.

[17] R.S. Marshall, J.R. Festa, Y.K. Cheung, R. Chen, M.A. Pavol, C.P. Derdeyn, et al., Cerebral hemodynamics and cognitive impairment: baseline data from the RECON trial, Neurology. 78 (2012) 250–255.

[18] M. Silvestrini, I. Paolino, F. Vernieri, C. Pedone, R. Baruffaldi, B. Gobbi, et al.,

Cerebral hemodynamics and cognitive performance in patients with asymptomatic carotid stenosis, Neurology. 72 (2009) 1062–1068.
[19] L. Buratti, C. Balucani, G. Viticchi, L. Falsetti, C. Altamura, E. Avitabile, et al., Cognitive deterioration in bilateral asymptomatic severe carotid stenosis, Stroke. 45 (2014) 2072–2077.
[20] A.V. Alexandrov, M.A. Sloan, C.H. Tegeler, D.N. Newell, A. Lumsden, Z. Garami, et al., American Society of Neuroimaging Practice Guidelines Committee, Practice standards for Transcranial Doppler (TCD) ultrasound: part II: clinical indications and expected outcomes, J. Neuroimaging 22 (2012) 215–224.
[21] O. Kargiotis, A. Safouris, G. Magoufis, M. Georgala, A. Roussopoulou, E. Stamboulis, et al., The role of neurosonology in the diagnosis and management of patients with carotid artery disease: a review, J. Neuroimaging 28 (2018) 239–251.
[22] R.S. Marshall, I. Asllani, M.A. Pavol, Y.K. Cheung, R.M. Lazar, Altered cerebral hemodyamics and cortical thinning in asymptomatic carotid artery stenosis, PLoS One 12 (2017) e0189727.
[23] J. Fierstra, D.B. Maclean, J.A. Fisher, J.S. Han, D.M. Mandell, J. Conklin, et al., Surgical revascularization reverses cerebral cortical thinning in patients with severe cerebrovascular steno-occlusive disease, Stroke 42 (2011) 1631–1637.
[24] S.E. Vermeer, T. Den Heijer, P.J. Koudstaal, M. Oudkerk, A. Hofman, M.M. Breteler, Rotterdam Scan Study, Incidence and risk factors of silent brain infarcts in the population-based rotterdam scan study, Stroke. 34 (2003) 392–396.
[25] M. Habes, G. Erus, J.B. Toledo, T. Zhang, N. Bryan, L.J. Launer, et al., White matter hyperintensities and imaging patterns of brain ageing in the general population, Brain. 139 (2016) 1164–1179.
[26] A.J.P.O. de Almeida, T.P. Ribeiro, I.A. de Medeiros, Aging: molecular pathways and implications on the cardiovascular system, Oxidative Med. Cell. Longev. 2017 (2017) 7941563.
[27] A. Harvey, A.C. Montezano, R.M. Touyz, Vascular biology of ageing-implications in hypertension, J. Mol. Cell. Cardiol. 83 (2015) 112–121.
[28] M. Plessers, I. Van Herzeele, F. Vermassen, G. Vingerhoets, Neurocognitive functioning after carotid revascularization: a systematic review, Cerebrovasc. Dis. Extra. 4 (2014) 132–148.
[29] R.N. Jones, Practice and retest effects in longitudinal studies of cognitive functioning, Alzheimers Dement. (Amst). 1 (2015) 101–102.