ESTABLISHING ECHOCARDIOGRAPHIC AND ARTERIAL STIFFNESS MARKERS AS PREDICTORS OF COGNITIVE DECLINE

F. MITU[1], MANUELA PADURARIU[1], CATALIN JOACABINE[1], A. CIOBICA[2,3] and
ROXANA CHIRITA[1]

[1]*"Gr. T. Popa" University of Medicine and Pharmacy,* 700115, Iasi, Romania
[2] *"Alexandru Ioan Cuza" University,* Iasi, 700506, Romania
[3]*Center of Biomedical Research of the Romanian Academy,* Iasi Branch, Romania

Abstract - Different factors seem to contribute to cognitive impairment in the elderly population. It is unclear which cardiovascular risk factors are the most significant contributors to cognitive decline. Although there is some recent neuropathological evidence that vascular lesions and atherosclerotic occlusion of the cerebral arteries may unmask or strengthen the clinical expression of cognitive decline and dementia, there is still little knowledge about the relevance of echocardiographic and arterial stiffness markers as predictors for cognitive decline. In the present study we decided to investigate whether and how the severity of cognitive impairment could be related to cerebral hemodynamic impairment, as well as the possible contribution of the alterations in cerebral hemodynamics (as expressed through some echocardiographic and arterial stiffness markers) to the progression of cognitive decline in a group of patients with cognitive impairments, as compared to a control group with no cognitive deficits. The main finding of our study indicated significant differences in terms of echocardiographic and arterial stiffness markers between the two groups, one composed of patients with cognitive impairment and one with normal-cognitive patients, which suggests an association between these parameters and poor cognitive function. While these functional changes of the cerebral vessel functions could have an important role in the pathogenesis of dementia, the identification of simple and accurate measures that are acceptable to patients and can serve as indicators of current cognitive impairment or the risk of cognitive decline could be very helpful in developing long-term preventive and therapeutic treatments for these patients.

Key words: Echocardiographic, arterial stiffness, markers, cognitive decline

INTRODUCTION

Different factors seem to contribute to cognitive impairment in the elderly population. A series of classical cardiovascular risk factors has been associated with the impairment of cognitive functions, such as hypertension, cholesterol or diabetes, suggesting a possible role in the etiopathogenic processes of dementia (Ciobica et al., 2011a, Joacabine et al., 2012). Still, it is unclear which cardiovascular risk factors are the most significant contributors to cognitive decline (Isaac et al., 2011, Vicario et al., 2011, Miralbell et al., 2010).

Although recent neuropathological evidence that vascular lesions and atherosclerotic occlusion of the cerebral arteries can unmask or strengthen the clinical expression of cognitive decline and dementia (Roher et al., 2003, Silvestrini et al., 2006), there is still little knowledge about the relevance of echocardiographic and arterial stiffness markers as predictors of cognitive decline.

The current hypothesis that vascular and degenerative processes may interact in expressing cognitive decline is a controversial issue (Langa et al., 2004, Silvestrini et al., 2006). Furthermore, the prevention of cognitive decline, manifested especially as dementia, has turned into a major public health challenge, with enormous pressure on identifying older people at risk and/or suffering from cognitive impairment who could benefit from preventive therapeutic interventions aimed at slowing down the cognitive decline (Hanon et al., 2005).

In the present study we used as a starting point the idea that arterial stiffness, which is a consequence of atherosclerosis, could be used as a potential marker to predict cognitive decline, considering that the progression of atherosclerosis is involved in cognitive impairment, and that prevention of atherosclerosis can be effective in this direction, although the exact associations between atherosclerosis and cognitive function have not yet been definitively determined (Fukuhara et al., 2006).

Considering that it is still unclear whether these markers are directly related to the appearance of cognitive decline, in the present report we decided to study whether and how the severity of the cognitive impairment could be related to cerebral hemodynamic impairment, as well as the possible contribution of alterations in cerebral hemodynamics (as expressed through some echocardiographic and arterial stiffness markers) to the progression of cognitive decline in a group of patients with cognitive impairments, as compared with a control group with no cognitive deficits.

PATIENTS AND METHODS

Clinical assessments

We enrolled 94 individuals from the patients who presented memory complaints during 2010-2011 at the Socola Psychiatry Hospital in Iasi. Selection of patients was performed by a neurologists and a psychiatrist with certified experience in managing patients with dementia after careful evaluation of clinical and instrumental examinations.

Patients older than 50 years, regardless of sex, marital or social status were included. The subjects had to be literate and without sensorial impairment. We excluded patients with acute comorbidities, chronic unstable diseases, except cardiovascular and metabolic dysfunction, as well as patients with other medical conditions that could lead to cognitive deficits. E.g. we excluded patients with chronic pulmonary problems such as TBC and sleep apnea, hypothyroidism, brain infarcts or head injury.

The clinical assessment included medical and family history, physical, neurological and psychiatric examination.

In addition, for BMI determination we divided the weight in kilograms by the height, measured in meters squared. Blood pressure was measured in the right arm after participants had been seated for five minutes. Blood samples were obtained in the morning before breakfast, allowed to clot and centrifuged immediately. Sera were aliquoted into Eppendorf tubes and stored at -80°C until determination of serum total cholesterol concentrations, which was performed in the hospital laboratory.

Neuropsychological assessment

The cognitive testing was performed in the morning, between 10-12 a.m., the patients having been told not to consume any stimulants the morning of the examination, such as coffee or smoking. The neuropsychological assessment was performed by a trained neuropsychologist who was blind to the results of hemodynamic evaluations.

At the same time, the patients were clinically evaluated for cardiovascular risk factors such as alcohol consumption, smoking and diabetes mellitus.

All included patients or caregivers gave written informed consent according to the Declaration of Helsinki. The study was approved by the local ethical committee.

We selected the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) scales in order to differentiate the subjects with cognitive impairment (CI group) from those without cognitive impairment. The CI group included subjects with scores less than or equal to 24 points in the MMSE test and a score less than or equal to 25 in the MoCA test (Folstein et al., 1975).

The hemodynamic parameters were determined through transcranial Doppler ultrasonography and performed by a physician blind to the cognitive evaluation.

Data analysis

The results for these vascular risk factors were analyzed using one-way analysis of variance (one-way ANOVA). All results are expressed as mean ± SEM. F values for which $p < 0.05$ were regarded as statistically significant.

RESULTS

Demographic data

As mentioned above, the mean age of the selected group was 63±9.8 years (i.e. 50-83 years-old) with 58.4% men and 53.1% having a rural background. 69.64 % were in a sexual relationship with only 10% employed and 83.3% being retired. The mean age of education was 8.4±3.4 and all the subjects were literate. The majority of the subjects were coffee consumers (83.3%), 40.4% were active smokers, while 29% reported chronic alcohol use (Table 1).

Adiposity was estimated by calculating BMI. We found a mean value for BMI of 25.9±2 and the majority of the individuals were overweight or obese (73.41%); 38.46% of the subjects had hyperlipidemia with a cholesterol mean of 217.5±11.9 mg/dl and 142.71±83.4 mg/dl for triglycerides; 73.4% were found to have hypertension while 11 individuals had diabetes mellitus. Regarding the history of stroke, 8.51% of the subjects reported an ischemic stroke more than 1 year before, while 21.27% had an

ischemic heart condition. Twenty-one patients reported physical exercise more than twice a week.

Table 1. Clinical characteristics of the subjects.

Crt	CI	NCI
N	74	20
Age (years)	63.8±8.4	56.1±4.7
Sex (%M)	40.5%	54.5%
Urban (%)	54.3%	50%
Marital status (single %)	32.3%	30%
Education (years)	7.93±3.2	10.7±2.1
Smoking (%)	32.3%	55.6%
Alcohol (%)	20%	22.2%
BMI (kg/m2)	27.04±3.9	23.7±4.8
Systolic BP (mmhg)	140.8±17.6	132.4±15.6
Diastolic BP (mmhg)	80.6±10.4	76,3±9.2
Cholesterol (mg/dl)	216,3±46,6	145,4±91,4
Triglyceride (mg/dl)	210,2±45,3	149,5±45
Glycemia (mg/dl)	93.6±25.33	77,9±9
LDL (mg/dl)	86.8±42.9	65.83±29
HDL (mg/dl)	51.1±13.6	49.13±18.3

Values are expressed as means ± SD and percent. BMI=body mass index; BP=blood pressure; LDL=Low-density lipoprotein; HDL=High-density lipoprotein

Echocardiographic measurements

The results of the echocardiographic measurements, which included the left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), interventricular septal end-diastolic dimension (IVSd), left ventricular end-diastolic posterior wall dimension (LVPWd), left ventricle mass (LVM), ejection fraction (EF), fractional shortening (FS), left atrial dimension (LA), aortic ring (AR), ascending aorta (AA), E velocity (EV), A velocity (AV), are presented in Table 2. As can

be seen, significant differences were observed between the cognitive impaired group and the control patients (non-cognitive impaired group) for all the aforementioned echocardiographic factors, except RVEDD (Table 2). This strongly suggests that these factors could be significant predictors of decreased cognitive functioning.

Table 2. Echocardiographic parameters.

	Control (Mean±SD)	Cognitive impairment (Mean±SD)	P
LVEDD (mm)	45.27±4.2	52.66±3.7	0.02*
LVESD (mm)	30.5±3.6	35.2±9.7	0.05*
IVSd (mm)	11.27±2.1	12.7±0.5	0.001**
LVPWd (mm)	11.54±1.5	12.5±1	0.0001**
LVM (g)	221.63±47.6	322.25±44.1	0.001**
EF%	61.36 ±8.3	57±18.1	0.008*
FS%	32.6±5	31±11.4	0.01*
LA (mm)	31.33±2.2	37.75±7.27	0.002*
RVEDD (mm)	25.71±3.6	28.5±7.7	0.12
AR (mm)	24.8±3.5	26.5 ±1.3	0.001**
AA (mm)	31.3±5.3	34±5.2	0.001**
EV (m/s)	0.55±0.1	0.49±0.2	0.04*
AV (m/s)	0.6±0.1	0.65±0.7	0.04*
E/A	0.93±0.3	0.76±0.3	0.04*

The values are expressed as mean±standard deviation, *p≤0.05, **p≤0.001. LVEDD=left ventricular end-diastolic dimension; LVESD=left ventricular end-systolic dimension; IVSd=interventricular septal end-diastolic dimension; LVPWd=left ventricular end-diastolic posterior wall dimension; LVM=*left ventricle mass;* EF=*ejection fraction;* FS=fractional *shortening;* LA=left atrial dimension; AR=aortic ring; AA=*ascending aorta;* EV=*E velocity;* AV=*A velocity.*

Vascular Doppler

Regarding vascular Doppler results, we focused on the following arteriographic indices: brachial augmentation index (Aixbr), aortic augmentation index (AIXao), pulse wave velocity (PWV), aortic pulse pressure (PPao), aortic systolic blood pressure (SBPao), brachial systolic blood pressure (SBP) and ankle brachial pressure index (ABPI) (Table 3).

We found very significant differences between the group of patients with cognitive impairment and those without, except in the case of Aixbr and AIXao (Table 3), confirming that these parameters have a fundamental importance as markers for predicting cognitive decline.

This was also confirmed by the results of carotid and vertebral artery analysis (both right and left) for the systolic/diastolic velocity and resistance index (Table 4), which exhibited very significant differences between the cognitive-impaired group and the control group, confirming an association between impaired cerebral vessel functionality and an unfavorable evolution of cognitive function.

DISCUSSION

Our findings revealed significant differences in terms of echocardiographic and arterial stiffness markers between the two groups we studied, one was comprised of patients with cognitive impairment and one without cognitive impairment. This suggests an association between these parameters and poor cognitive function. Our data further suggest a contribution of these vascular factors to the pathogenesis of cognitive impairment-related disorders. The results are also consistent with some previous findings suggesting that vascular disorders play an important role in cognitive impairment (Hanon et al., 2005).

Johnson et al. (2010) demonstrated in a recent study some significant correlations between cognitive functions and the ankle-brachial index, which is known as a marker of generalized atherosclerosis, myocardial infarction and stroke (Heald et al.,

Table 3. Arteriographic parameters.

N	AIxbr (%)	AIXao (%)	PWVao (m/s)	PPao (mmHg)	SBPao (mmHg)	ABPI dr	ABPI stg
Control (Mean±SD)	18.85± 29	47.17± 14.7	9.5± 1	51.2± 8.4	128± 12	0.95± 0.3	1.01± 0.08
Cognitive impairment(Mean±SD)	-2.3± 22.4	19.7±12.3	7.26±1.5	44±15	106.6±21.8	1±0.1	1.06±0.2
P	0.9	0.2	0.01*	0.01*	0.01*	0.008*	0.001**

Data are expressed as means +/-SD, p*≤0.05, p**≤0.001. Aixbr= brachial augmentation index; AIXao=aortic augmentation index; PWV=pulse wave velocity; PPao=aortic pulse pressure; SBPao=aortic systolic blood pressure; SBP=brachial systolic blood pressure; ABPI= ankle brachial pressure index.

Table 4. Carotid and vertebral artery analysis (both right and left) for the systolic/diastolic velocity and resistance index.

		Right Common Carotid Artery	Right Internal carotid artery	Right External carotid artery	Right Vertebral artery	Left Common Carotid Artery	Left Internal carotid artery	Left External carotid artery	Left Vertebral artery
Systolic velocity	Control	55.3±8.5	43.33±9	59.77±17.8	29±8.19	53.55±11.3	47.22±15.7	47.88±15.2	31.75±3.6
	Cognitive impairment	53.8±11.5	40.66±5.8	52.83±6.2	33.33±12.75	50±11.1	47.5±15.6	48.16±8.4	30.66±9.6
	P	<0.0001	<0.0001	<0.0001	0.001	<0.0001	0.001	0.001	0.01
Diastolic velocity	Control	17.8±6	18.11±5.7	17.33±7.4	13.5±4.6	8±5.4	22.33±7.2	17.44±7	15.5±2.7
	Cognitive impairment	14.5±2.5	15.16±3.7	14±3.9	15±4.8	5±4.4	20.33±5.2	12.33±4.2	15.33±5.4
	P	<0.0001	<0.0001	<0.0001	0.01	<0.0001	<0.0001	0.01	0.01
Resistance index	Control	0.67±0.08	0.59±0.08	0.71±0.07	0.55±0.09	0.63±0.08	0.52±0.05	0.63±0.09	0.5±0.1
	Cognitive impairment	0.72±0.05	0.62±0.72	0.74±0.05	0.52±0.08	0.68±0.03	0.56±0.04	0.74±0.08	0.5±0.06
	P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

2006). Also, a reference study in this area of research by Hanon et al. (2005), which showed a significant relationship between arterial stiffness and the cognitive impairment, suggests that functional changes of the arterial system could be involved in the onset of dementia. Fukuhara et al. (2006) demonstrated that it could be possible to predict cognitive functions based on arterial stiffness, as assessed by pulse wave velocity in very old patients. The Rotterdam Study demonstrated that the presence of atherosclerotic plaques or wall thickening of the carotid artery were significantly associated with vascular dementia and Alzheimer's disease (Hofman et al., 1997).

The aforementioned results could be very important since these factors are relatively easy to assess and are noninvasive, providing reliable information about the atherosclerotic conditions associated with poor cognitive function. Thus, they could represent a low-cost and perhaps effective way of gathering a general indicator of overall cognitive function (Fukuhara et al., 2006, Johnson et al., 2010).

Regarding the possible mechanism implicated in this, some of the cited mechanisms could be represented by cerebrovascular lesions, white matter changes and pre-existent asymptomatic Alzheimer's brain lesions (Hanon et al., 2005), as well as cerebral amyloid angiopathy, arteriolosclerosis, capillary endothelial and basement membrane changes (Silvestrini et al., 2006). With regard to the mechanics, it seems that endothelial lesions in Alzheimer's disease have a close relationship with senile plaques (Kalaria et al., 1996). Additionally, the specific BETA-amyloid compound could be very closely related to the vascular endothelial cells producing free radicals and increasing oxidative stress (Thomas et al., 1996, Hanon et al., 2005). We previously demonstrated that the central oxidative stress is very important in affecting cognitive functions and most neuropsychiatric disorders (Padurariu et al., 2010, Ciobica et al., 2011b,c, 2012, Stefanescu et al., 2012, Irimia et al., 2013). Moreover, it seems that endothelial nitric oxide (NO) is implicated in this matter, which also leads us to possible correlations that might exist between oxidative and nitrosative stress in generating various vascular alterations (Bild et al., 2013a).

Other relevant aspects are represented by the fact that arterial stiffness increases in patients with diabetes (Airaksinen et al., 1993) and end-stage renal disease (London et al., 1990, Fukuhara et al., 2006). The possibility of influencing cerebral vessel functions through specific therapeutics leads to the idea of using angiotensin-converting enzyme inhibitors to reduce the cognitive deterioration of subjects. The very relevant European study called Systolic Hypertension in the Elderly in Europe (Syst-Eur), has demonstrated that antihypertensive medications could reduce the incidence of all types of dementia (Forette et al., 2002). Our group has also recently demonstrated that the administration of an angiotensin-converting enzyme inhibitor (captopril) in rats results in significant cognitive improvements and decreased central oxidative stress (Bild et al., 2013b).

CONCLUSIONS

We demonstrate the possibility of obtaining, through some simple evaluations of cerebral vessel functions, a range of very useful information for the identification of cognitive decline in patients who are at significant risk of a rapid and pronounced evolution of dementia. While these functional changes in the arterial system could have an important role in the pathogenesis of dementia, the identification of simple and accurate measures that are acceptable to patients and can serve as indicators of current cognitive impairment or the risk of cognitive decline could be very helpful in developing long-term preventive and therapeutic strategies for these patients.

REFERENCES

Airaksinen, K.E., Salmela, P.I., Linnaluoto, M.K., Ikaheimo, M.J., Ahola, K. and L.J. Ryhanen (1993). Diminished arterial elasticity in diabetes: Association with fluorescent advanced glycosylation end products in collagen. *Cardiovasc Res* **27**, 942-945.

Bild, W., Ciobica, A., Padurariu, M. and V. Bild (2013a). The interdependence of the reactive species of oxygen, nitrogen and carbon. *Journal of Physiology and Biochemistry* **69**, 147-154.

Bild, W., Hritcu, L., Stefanescu, C. and A. Ciobica (2013b). Inhibition of central angiotensin II enhances memory function and reduces oxidative stress status in rat hippocampus. *Progress in Neuropsychopharmacology & Biological Psychiatry* **43**, 79-88.

Ciobica, A., Olteanu, Z., Padurariu, M. and L. Hritcu (2012). The effects of low-dose pergolide on memory and oxidative stress in a 6-OHDA induced rat model of Parkinson's disease. *Journal of Physiology and Biochemistry* **68**, 59-69.

Ciobica, A., Padurariu, M., Bild, W. and C. Stefanescu (2011a). Cardiovascular risk factors as potential markers for mild cognitive impairment and Alzheimer's disease. *Psychiatr Danub* **23**, 340-6.

Ciobica, A., Padurariu, M., Dobrin, I., Stefanescu, C. and R. Dobrin (2011b). Oxidative stress in schizophrenia - focusing on the main markers. *Psychiatr Danub* **23**, 237-45.

Ciobica, A., Bild, V., Hritcu, L., Padurariu, M. and W. Bild (2011c). Effects of angiotensin II receptor antagonists on anxiety and some oxidative stress markers in rat. *Central European Journal of Medicine* **6**, 331-340.

Folstein, M.F., Folstein, S.E. and P.R. McHugh (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* **12**, 189-98.

Forette, F., Seux, M-L., Staessen, J.A., Thijs, L., Babarskiene, M-R., Babeanu, S. et al. (2002). The prevention of dementia with antihypertensive treatment. New evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* **162,** 2046-2052.

Fukuhara, M., Matsumura, K., Ansai, T., Takata, Y., Sonoki, K., Akifusa, S. et al. (2006). Prediction of cognitive function by arterial stiffness in the very elderly. *Circ J* **70**, 756-61.

Hanon, O., Haulon, S., Lenoir, H., Seux, M.L., Rigaud, A.S., Safar, M. et al. (2005). Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke* **36**, 2193-7.

Heald, C.L., Fowkes, F.G.R., Murray, G.D. and *J.F. Price* (2006). Risk of mortality and cardiovascular disease associated with the ankle–brachial index: systematic review. *Atherosclerosis* **189**: 61-69.

Hofman, A., Ott, A., Breteler, M.M., Bots, M.L., Slooter, A.J., van Harskamp, F. et al. (1997). Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* **349**, 151–154.

Irimia, R., Ciobica, A., Stanciu, C. and *A. Trifan* (2013). The relevance of oxidative stress in cirrhotic patients with different forms of hepatic encephalopathy. *Arch. Biol. Sci., Belgrade* **65**.

Isaac, V., Sim, S., Zheng, H., Zagorodnov, V., Tai, E.S. and *M. Chee* (2011). Adverse associations between visceral adiposity, brain structure, and cognitive performance in healthy elderly. *Front Aging Neurosci* **3**:12.

Joacabine, C., Padurariu, M., Ciobica, A., Dobrin, R., Popescu, C.D. and *F. Mitu* (2012). The association between cholesterol levels and brachial/aortic augmentation index versus cognitive status in patients with cardiovascular risk factors. *Arch. Biol. Sci., Belgrade* **64**, 419-426.

Johnson, W., Price, J.F., Rafnsson, S.B., Deary, I.J. and *F.G. Fowkes* (2010). Ankle-brachial index predicts level of, but not change in, cognitive function: the Edinburgh Artery Study at the 15-year follow-up. *Vasc Med* **15**, 91-7.

Kalaria, R.N. and *P. Hedera* (1996). Beta-Amyloid vasoactivity in Alzheimer's disease. *Lancet* **347**, 1492-1493.

Langa, K.M., Foster, N.L. and *E.B. Larson* (2004). Mixed dementia. Emerging concepts and therapeutic implications. *J Am Med Assoc* **292**, 2901-2908.

London, G.M., Marchais, S.J., Safar, M.E., Genest, A.F., Guerin, A.P., Metivier, F. et al. (1990). Aortic and large artery compliance in end-stage renal failure. *Kidney Int* **37**, 137-142.

Miralbel, J., Soriano, J.J., López-Cancio, E., Arenillas, J.F., Dorado, L., Barrios, M. et al. (2010). Vascular risk factors and cognitive performance in patients 50 to 65 years-old. *Neurologia* **25**, 422-9.

Padurariu, M., Ciobica, A., Hritcu, L., Stoica, B., Bild, W. and *C. Stefanescu* (2010). Changes of some oxidative stress markers in the serum of patients with mild cognitive impairment and Alzheimer's disease. *Neuroscience Letters* **469**, 6-10.

Roher, A.E., Esh, C., Kokjohn, T.A., Kalback, W., Luehrs, D.C. and *J.D. Seward* (2003). Circle of Willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler Thromb Vasc Biol* **23**, 2055-2062.

Silvestrini, M., Pasqualetti, P., Baruffaldi, R., Bartolini, M., Handouk, Y., Matteis, M. et al. (2006). Cerebrovascular reactivity and cognitive decline in patients with Alzheimer disease. *Stroke* **37**, 1010-5.

Stefanescu, C. and *A. Ciobica* (2012). The relevance of oxidative stress status in first episode and recurrent depression. *Journal of Affective Disorders* **143**, 34-8.

Thomas, T., Thomas, G., McLendon, C., Sutton, T. and *M. Mullan* (1996). Beta-Amyloid mediated vasoactivity and vascular endothelial damage. *Nature* **380**:168-171.

Vicario, A., del Sueldo, M.A., Zilberman, J.M. and *G.H. Cerezo* (2011). Cognitive evolution in hypertensive patients: a six-year follow-up. *Vasc Health Risk Manag* **7**, 281-5.