

Executive dysfunction in middle-aged hypertensive adults

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Abstract

Objective: The objective was to compare the executive functions between hypertensive and non-hypertensive middle-aged Mexican adults. **Methods:** An observational and analytic study was designed. Participants were men and women residents of Southeastern Mexico, aged between 40 and 60 years, with at least 5 years of hypertension diagnosis. The control group was people without hypertension. All participants completed a digit symbol substitution test (DSST), clinical and epidemiological data. Statistical analysis unpaired Student's t-test, $p < 0.05$. **Results:** DSST score in control men was 37.78 ± 11.94 , control women: 42.96 ± 11.19 , hypertensive men: 16.81 ± 9.82 , and hypertensive women: 26.88 ± 12.04 . Significant differences were found between hypertensive and non-hypertensive groups. Men had worse scores than women. No difference between normotensive men and women. Inverse correlation was found between DSST score and age, values of systolic and diastolic blood tension in the hypertension group. **Conclusion:** Hypertension decreases the executive function in middle-aged people, mainly in men. This dysfunction could be an early indicator of brain deterioration.

Key words: Hypertension. Executive cognitive function. Mature age. Brain dysfunction.

Disfunción ejecutiva en adultos hipertensos de edad madura

Resumen

Objetivo: comparar la función ejecutiva entre adultos mexicanos de mediana edad, hipertensos y no hipertensos. **Métodos:** se diseñó un estudio observacional y analítico. Los participantes eran hombres y mujeres residentes del sureste de México, con edades comprendidas entre 40 y 60 años y al menos cinco años de diagnóstico de hipertensión. Los controles fueron personas sin hipertensión. Todos los participantes completaron la prueba de Sustitución de Símbolo y Dígitos (DSST), datos clínicos y epidemiológicos. Análisis estadístico t-Student no pareada, $p < 0.05$. **Resultados:** la puntuación DSST en los hombres control fue de 37.78 ± 11.94 y las mujeres control: 42.96 ± 11.19 , los hombres hipertensos: 16.81 ± 9.82 y las mujeres hipertensas: 26.88 ± 12.04 . Se encontraron diferencias significativas entre el grupo hipertenso y no hipertenso. Los hombres tuvieron peores puntajes que las mujeres. No hay diferencia entre hombres y mujeres normotensos. Se encontró correlación inversa entre la puntuación DSST y la edad, los valores de tensión arterial sistólica y diastólica en el grupo con

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hipertensión. **Conclusión:** la hipertensión disminuye la función ejecutiva en personas de mediana edad, principalmente en hombres. Esta disfunción podría ser un indicador temprano de deterioro cerebral.

Palabras clave: Hipertensión. Función cognitiva ejecutiva. Edad madura. Disfunción cerebral.

Introduction

According to the National Health Survey (ENSANUT MC) 2016, 25.5% of Mexican adults have hypertension^{1,2}. Hypertension causes functional and structural alterations in blood vessels, especially affecting arteries of medium and small caliber, which predominate in some organs like brain³. Several studies have established a causal relationship between hypertension and brain diseases such as stroke, vascular dementia, and recently Alzheimer's disease⁴. Due to factors that are not yet completely clear, vascular damage induced by hypertension seems to be more aggressive in the frontal lobe, which could lead to executive dysfunction⁵.

Executive functions refer to a collection of cognitive abilities that enable and drive adaptive, goal-oriented behavior. These include the ability to generate thought and think flexibly, to update and manipulate information mentally, to inhibit what is irrelevant to current goals, to self-monitor, and to plan and adjust behavior as appropriate to the present context. Executive dysfunction impairs efficient performing of daily activities and increases the risk of morbidity and mortality by accidents inside and outside the home, increases dependence on caregivers, limits productive activities, and reduces quality of life^{6,7}. Chronicity and aging can worsen brain damage caused by hypertension⁸. Executive dysfunction may be one of the first manifestations of brain damage⁹, especially in patients who do not achieve control despite consuming pharmacological treatment¹⁰.

In most cases, brain damage is irreversible⁶, so it is an important early diagnosis. Young and middle-aged hypertensive people usually have not symptoms of a cognitive impairment, however, there are standardized tools to evaluate the executive function¹¹. The aim of this study was to compare the executive cognitive function in middle-aged hypertensive and no hypertensive Mexican adults and related with some epidemiological data.

Methods

It is an observational and analytical study.

Patients were recruited at the Unit of Social Insertion (UUIS) of University of Yucatán, México. This institution

provides medical care to approximately 1179 users annually. The sample size was non-probabilistic and included all patients with and without hypertension, men and women from 41 to 60 years, with and without diagnosis of hypertension, and with minimum secondary schooling who attended the external consultation from October 2018 to December 2018. All selected patients with hypertension had at least 5 years of diagnosis to ensure chronicity period. To avoid biases on interpretation of cognitive function, results were excluded patients with a history of cerebral vascular event, known brain diseases, with obesity (body mass index [BMI] > 30), dyslipidemias, and hypo or hyperthyroidism. Motor, visual or auditory dysfunction, or under neurological or psychiatric treatment were not included in the study. Ninety-two people agreed to participate and met the selection criteria.

We eliminated patients who at the time of the evaluation had mild cognitive deterioration and/or depressive symptomatology. Seven people were eliminated due to symptoms of depression and/or cognitive impairment. Forty-one hypertensive and 44 normotensive patients were included in final analysis.

Procedures

A physician in a clinic room evaluated patients, during the morning (8-10 am). A brief clinical history was complete emphasizing aspects related to hypertension, time of hypertension evolution, type of treatment it carries, drugs, doses, and achievement of therapeutic goal. All participants in fasting were weighed and measured, without shoes, trousers or skirts, and shirt or blouse. The patients were weighed and measured with Detecto® brand stadiometer and scale; with these values, the BMI was determined, according to the following formula: weight (Kg)/Size (M²).

Blood pressure (BP) was determined with a Check-ATeK® Baumanometer calibrated according to the official Mexican standard NOM-009-SCFI-1993 with the technique and specifications indicated by NOM-030-SSA2-2017¹². It was considerate as therapeutic goal if patient at time of measurement systolic BP (SBP) < 140 mmHg and diastolic < 90 mmHg. If in the past 3 months, average arterial BP would not

have exceeded reference values (taken from the clinical record), patients were considered controlled.

Questionnaires

1. Digit symbol substitution test (DSST) evaluates the working memory, organization of perceived stimuli, visomotor coordination, and selective attention, which are executive cognitive functions. DSST was validated in Europe and the United States, mainly in the older adult population. Due to its iconographic nature, no linguistic translation is required, and the test has been used and validated in multiple contexts, regions, and languages, including Spanish and Mexican population¹³⁻¹⁵. All participants were explained how to respond and used as an example the first 10 boxes with their respective symbols to ensure that patient understood how to perform the test. Participant had to match numbers with their respective symbol in order and without skipping any box, as fast as possible and without any kind of external help. Test had a total duration of 90 s (in triplicate). The number of binomials number-symbol paired correctly constituted score of the participant in the DSST. Blank space between two completed items does not invalidate the test; however, two or more consecutive blank spaces point to the end of the test. Paired symbols after two or more blank spaces are not considered in total score. DSST has no cutting points, score constitutes a continuous variable and has no individual value; it takes utility at population level when different groups are compared and is also useful when applied in the same individual overtime. Score reflects the speed of information processing as an executive function, and in comparison with other cognitive tests, DSST performance is strongly correlated with the volume of the prefrontal cortex¹⁶.
2. Mini-mental state examination (MMSE): this is widely validated tool, values in < 10 min cognitive state examining functions such as the ability to record, attention, calculus, memory, language, ability to follow simple instructions, and guidance. MMSE is used primarily to detect patients with mild cognitive impairment and other more severe forms of cognitive deterioration. Cutting point < 25 was an elimination criterion¹⁷.
3. Beck-II depression inventory (BDI-II): BDI-II requires 5-10 min to be completed and it explores data of major depression in the past 2 weeks, consistent with DSM-5 criteria. Depression has significant repercussions on global cognitive function and can

affect test results such as DSST, so score > 19 (of a maximum of 63) was an elimination criterion¹⁸.

The procedures were the same for the control group (not hypertensive), only the interrogation on arterial hypertension was excluded from the study.

Ethical considerations

The study was carried out in accordance with the provisions of the General Law on Health in the field of research, Mexican Secretariat of Health 1987. Ethical principles of the Helsinki World Medical Assembly and The International Code of Medical Ethics, as well as the provisions and Guidelines of the National Bioethics Commission (Conbioetica) 2016, were attended too. The project was evaluated and approved by the Ethics and Research Committee of the UUIS of the Autonomous University of Yucatán.

Statistical analysis

It was carried out with the statistical program Graph-Pad Prism 7[®]. The normality of the data was determined with the Shapiro-Wilk test. We compared the values of the scores of DSST with values of BP, age, duration of hypertension, using Student's t-test for unrelated samples. For variables: sex, therapeutic status, and Chi-square test were used. Linear correlation was performed with hypertension length, age, SBP, and diastolic blood pressure (DBP) related to the DSST score. The statistical significance was 95%, $p < 0.05$.

Results

The results presented below correspond to 85 adults. Table 1 describes its main characteristics, grouped as a control group (not hypertensive) and hypertension group.

We found similar distribution of sex, age and BMI in both groups.

There were no differences in BP between men and women, neither in the hypertension group nor in the control group. DSST values in the hypertension group were lower than the control group. Hypertensive men performed less than women did ($p = 0.007$). In the control group, there was no sex difference ($p = 0.15$).

Diagnostic average duration in the hypertension group was 11.9 ± 5 years, on men was 11.31 ± 5.5 years and woman 12.28 ± 4.7 ($p = 0.55$). Most hypertensive patients (82.9%) were receiving some form of pharmacological treatment, 17% of patients had abandoned

Table 1. Characteristics and ejective function of adults with and without hypertension

Characteristic	Group		p
	Control (n = 44)	Hypertension (n = 41)	
Sex			
Female	61%	59%	0.99*
Male	39%	41%	
Age (years)	50.70 ± 6.70	52.50 ± 5.30	0.17
BMI (kg/m ²)	26.38 ± 1.98	27.07 ± 2.16	0.12
BP (mmHg)			
Systolic	115 ± 9.76	137.70 ± 16	< 0.001
Diastolic	74.32 ± 6.85	86.44 ± 10.71	
DSST			
Total group	40.84 ± 11.66	22.95 ± 12.16	< 0.001
Female	42.96 ± 11.95	26.88 ± 12.04	< 0.001
Male	37.78 ± 11.99	16.81 ± 9.82	< 0.001

*Chi-square.

Continuous variables represent the average ± the standard deviation. Categorical data are expressed as a percentage. The blood pressure (BP) value represents the average of three monthly measurements of each participant. Student's t-test statistical analysis for independent samples. BMI: body mass index; DSST: digit symbol substitution test.

Table 2. Comparison of controlled and uncontrolled hypertensive patients

Characteristic	Subgroup		p
	Controlled (41.4%)	Uncontrolled (58.6%)	
Sex			
Female	47.4%	58.6%	0.87*
Male	50%	50%	
BP (mmHg)			
Systolic	116.50 ± 10.57	144.20 ± 9.60	< 0.001
Diastolic	75.88 ± 7.12	83.75 ± 11.73	
Pharmacotherapy	100%	70.17%	0.02 [†]
DSST			
Total group	27.12 ± 12.23	20 ± 11.32	0.06

*Chi-square.

DSST: digit symbol substitution test. Student's t-test statistical analysis for independent samples. Continuous variables represent the average ± the standard deviation. Categorical data are expressed as a percentage. The blood pressure (BP) value represents the average of three monthly measurements of each participant.

treatment or had never consumed drugs for it. About 97% of patients with treatment were taking one drug, 3% taken two or more. About 76% consuming angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 11.7% were taking beta-blockers, and 12% receiving calcium antagonist or diuretics. Table 2 shows the results of controlled and uncontrolled hypertensive patients.

In the hypertension group, there was a negative correlation between the DSST score with age ($y = -1.139x + 82.76$, $R^2 = 0.24$, $p = 0.001$), with SBP ($y = -0.292x + 61.75$, $R^2 = 0.16$, $p = 0.008$), and DBP ($y = -0.357x + 51.69$, $R^2 = 0.09$, $p = 0.045$). No correlation was found between the DSST score and the duration of hypertension. The control group showed no correlation (data not shown).

Discussion

This study showed that hypertension in middle-aged Mexican adults is associated with lower scores in the DSST, a validated test with a high sensitivity to detect variations in executive function^{16,19}. Hypertension is a well-known risk factor for numerous adverse cardiovascular outcomes². Given their impact in brain vessels vasodilatory capacity, it could decrease biological efficacy to execute some cognitive functions³. Although

there is a normal increase in the BP while aging due to calcification and atherosclerosis, hypertension in younger subjects suggests a possible genetic predisposition negatively modulated by environmental and lifestyle factors such as obesity and elevated salt intake and others²⁰.

Mean duration of hypertension in participants in our study was higher than that reported by the National Health Survey, which states that most hypertensive individuals in Mexico had 4-10 years with the diagnosis¹. This could be explained by our selection criteria only allowed people with at least 5 years with hypertension. About 83% of hypertensive participants in our study had pharmacological treatment, similar with 79.3% reported in other studies for Mexican hypertensive patients¹. There is evidence that lack of pharmacological treatment in hypertensive people increases their risk of ischemic heart disease, heart failure, stroke, and kidney diseases²¹.

Although the treatment of hypertension is cheap and simple compared to other chronic diseases, their asymptomatic nature can cause patients to refuse to undergo lifelong treatment or reduce their adherence. Remarkably, only 50% of patients with treatment had achieved therapeutic goals. Mexican National Health Survey reported a hypertensive control proportion of 45.6%¹. Most hypertensive patients in our study consume antihypertensive drugs in monotherapy, and though this approach facilitates compliance, it is well documented that few patients achieve adequate

hypertensive control without two or more drugs^{22,23}. We observed an important number of patients receiving beta-blockers, which, according to recent guidelines should not be used as first choice antihypertensive drugs because they promote the development of dyslipidemias, impair glucose tolerance and hinder weight reduction^{23,24}. It is important to analyze individual patient conditions to offer the best treatment in each case and achieve therapeutic goals.

Our findings show that hypertensive patients have a worse performance in the DSST compared with normotensive people. Cognitive impairment is a gradual process and having hypertension could accelerate this process. Controversial results of the effect of hypertension on cognitive function have been found^{24,25}. In our study, SBP was responsible for 16% of the variance in DSST scores in the hypertensive patients.

Some studies have found a better executive performance in men²⁶; however, we found that men hypertensive obtained lower scores in DSST compared with woman hypertensive or normotensive people. There is evidence that in women, prenatal exposition to different hormonal concentrations promotes the overdevelopment of specific neuronal pathways and the neurotrophic effects of estrogens are well described²⁷. The patients in this study were around 50 years old, so the women were in the menopausal period; consequently, it is likely that they maintained some degree of neurotrophic estrogenic stimulation and better cerebral blood flow compared to man²⁸.

The mechanisms that regulate arterial BP are similar in men and women; however, there are physiological differences at the molecular, cellular, and tissue levels between the sexes that contribute to differences in disease onset, susceptibility, prevalence, and treatment responses. The sympathetic nervous system, the renin-angiotensin-aldosterone system, and the immune system are differentially activated in males and females. Sex hormones such as estrogens or testosterone as well as sex chromosome complement likely contribute to sex differences in BP and cardiovascular disease. At the cellular level, differences in cell senescence pathways may contribute to increased longevity in women and may limit brain damage caused by hypertension²⁹. Therefore, this may be an explanation because the women in our study were less affected in their executive function. In addition, many lifestyles and environmental factors such as smoking, alcohol consumption, and diet, they are usually different in men and

women, as well as their possible effect on BP and brain function, were not evaluated in the present study.

SBP and DBP were higher than those reported in the previous studies in Mexico¹, and higher BP readings were correlated with lower DSST scores. Uncontrolled hypertension increases vascular stiffness which rises pulse pressure. Increased BP is a risk factor for white matter lesions and subclinical hemorrhages that can cause cognitive alterations³⁰. In concordance with other authors³¹, we could not find differences in executive function between controlled or uncontrolled hypertensive patients, maybe due to the small sample size. Several studies have reported that an elevated BP during middle age predicts cognitive impairment 20-30 years later^{32,33} and SBP control since middle age reduces this risk^{27,34}.

Many studies have reported intense prefrontal activation during DSST resolution using functional MRI and electroencephalography^{35,36}, these areas are particularly vulnerable to subclinical ischemia because they depend on distal blood supply. Vasomotor dysfunction characteristic of hypertension impairs their capacity for compensatory redistribution of blood flow in response to cognitive challenge⁹. DSST is a powerful tool to explore the executive cognitive domain associated with brain regions most affected by hypertensive vasculopathy. On the hypertensive group, we found an inverse correlation between age and DSST performance, which is consistent with the previous reports^{21,37}. Motor dexterity decline through aging may contribute to this consistent finding and hypertension could accelerate this process. Although we guarantee a minimum level of education in our inclusion criteria, we did not specifically explore the influence of the educational level on DSST performance. However, the previous reports state that there is no relationship between education and DSST performance probably due to their iconographic nature, making it useful in poor educated populations like ours⁸. As opposed to most studies revised, we could not observe a significant correlation between DSST scores and duration of disease. The duration of hypertension is relevant because there is evidence that their neurodegenerative effects are accumulative³⁸.

Effective hypertension management requires a substantial amount of self-planning and adherence to pharmacological and non-pharmacological treatment. Thus, we propose that executive dysfunction may worsen self-care on hypertensive patients. Assessing executive function since middle age with easy administrated tests

like the DSST in primary health-care settings could promote early interventions that preserve the functional independence of hypertensive patients.

Conclusion

In conclusion, mature adults with hypertension had less efficiency in the executive function test. Men showed worse test performance compared to women. In this population the control of hypertension and the duration of the disease did not affect the performance of the executive function.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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