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Elderly Hypertensive Patients: Silent White Matter Lesions, Blood Pressure Variability, Baroreflex Impairment and Cognitive Deterioration

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Abstract: *Introduction*: Hypertension may increase the risk for stroke and is frequently associated with subcortical and periventricular white matter lesions (WML). This is considered a prognostic factor for the development of stroke and cognitive impairment, particularly in attention processes. Additionally, in elderly subjects, it is known the implications of alterations in the neural cardiovascular regulation and the cardiovascular risk.

Aims: To evaluate, in asymptomatic elderly hypertensives, the association of ambulatory blood pressure values and autonomic activity with neurocognitive impairment and WML. In addition, we also evaluated the role of the autonomic nervous system particularly the vagal component, in the pathogenesis of white matter lesions.

Methods: We studied 22 elderly essential hypertensive patients (69±1.1y) and as control group, 16 normotensive elderly subjects (age 67±3.2y) were also enrolled. To each one of them, a cerebral MRI was performed to classify them, by a neuro-radiologist blinded of the subject clinical status, using a 0 to 9 scale where 0 denoted no WML and 9 the most severe lesions.

Twenty four hours arterial blood pressure monitoring was performed to each one of the subjects under study. Office blood pressure was measured 3 times and the mean value reported. Beat to beat finger arterial pressure monitoring (Finapres) was performed for a 2h period. During the first hour the patient remained lying supine in a quiet darkened room and during the second hour four manoeuvres: stand-up, cold pressor test, handgrip and quiet activity were randomly performed. Mean blood pressure and pulse interval values, from the two periods, and their respective variabilities, baroreflex sensitivity and power spectral analysis were calculated.

Regarding neuropsychological assessment: Minimental test, attention evaluation, RAVLT, visual memory, language and executive function, geriatric depression scale, cognitive deficit rate tests were performed in all subject.

Results: We found a closer correlation of WML with 24hs ABPM than with office BP readings being more evident with systolic blood pressure during the night time period. WML failed to show any correlation with SBP average values derived from the Finapres recordings in either the supine or the upright position, while it was positively and significantly related to PP in both conditions. However, beat to beat SBP variability, either in the supine or in the upright position, showed a positive and significant correlation with WML.

During the resting period, BRS calculated through the sequence method (Time Domain) was similar in HT and NT subjects. However when BRS was assessed in the frequency domain a significant reduction was observed in HT compared with NT. In addition, At the time of laboratory manoeuvres implying sympathetic activation, BRS was significantly reduced as compared to the resting values being particularly evident for the HF values.

In hypertensive subjects, only semantic fluency showed a significant difference ($p=0.01$), when compared to normotensives. When the patients were divided in older and younger than 75 years, a significant difference was observed in the delayed analysis of words, and in the phonological fluency showing a significant higher rate of pathological results in the group of patients older than 75 years.

Conclusions: As previously shown, incidental WML, suggestive of silent cerebrovascular disease, is a frequent finding in elderly hypertensives. Night-time BP mean values and SBP variability in upright position seems to be the best predictor on silent cerebral WML. The vagal component of the autonomic nervous system seems to be involved in the pathogenesis of these lesions. Finally, the neurocognitive alterations are multifactorial in origin where the aging process seems to be the principal component.

Keywords: White matter lesion, elderly subjects, essential hypertension, autonomic function, variability and barorreflex control.

INTRODUCTION

It has been shown that hypertension may increase the risk for stroke and is frequently associated with subcortical and

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periventricular white matter lesions (WML) [1] that seems to be related to small vessel disease in the brain, especially asymptomatic cerebral ischemia [2]. Other risk factors associated, such as age, diabetes and hyperlipidemia [3], have been also related to this neurological outcome. In this way, the presence of WML is considered a prognostic factor for either stroke [4] or cognitive impairment [5], particularly in attention processes and speed of the information processing [6].

Organ damage due to hypertension is more closely associated with the average 24h blood pressure values obtained by ambulatory blood pressure monitoring than with the casual blood pressure readings obtained in the doctor's office [7]. The superiority of the 24h average blood pressure values over office readings has been demonstrated not only in confront to organ damage but also in the prediction of cardiovascular events rate [8, 9]. Furthermore, evidence showed that the level of blood pressure variability, during the day and night time periods, carry important clinical information and is independently related to hypertension organ damage and cardiovascular morbidity and mortality [10]. However, contradictory information has been reported in hypertension, regarding ambulatory blood pressure and neurocognitive deterioration or WML [11].

Other important aspect to be considered is the possible involvement of the autonomic nervous system in the pathogenesis of these lesions, particularly the vagal component which is known to be impaired in elderly individuals [12-14], and could explain the depressed baroreflex sensitivity accompanying the ageing process and the increasing cardiovascular risk in this elderly hypertensive population [15, 16].

In this paper we analyzed the possible relationship of brain matter lesions, neurocognitive impairment and the autonomic disturbances in blood pressure regulation in elderly hypertensive individuals.

METHODS

We evaluated 56 elderly patients (aged >65 years) referred to our clinic for hypertension screening. Twenty two of them were enrolled (10 males, age 69 ±1.1 years), while the remaining 34 were excluded because of either atrial fibrillation, clinically relevant stenosis of the internal carotid artery (<40 %), lack of informed consent, artefacts in the Finger BP recordings, claustrophobia or the incidental finding of pathological lesions in the brain by MRI.

The subjects were considered hypertensive (HT) when both the average of 3 consecutive office blood pressure measurements, performed with a mercury sphygmomanometer, was equal or higher than 140 and/or 90mmHg and the day-time mean ambulatory BP value equal or higher than 135 and/or 85 mmHg. At the time of the study patients had withdrawn any previous antihypertensive drug treatment since at least 2 week.

Major cardiovascular diseases and any possible cardiovascular source of cerebral emboli were excluded by transthoracic Doppler echocardiography followed, whenever indicated by the results of the clinical evaluation, by transesophageal echocardiography, cardiac nuclear imaging, cardiac catheterization and coronary angiography.

As a control group, we also enrolled 16 normotensive subjects (NT) of comparable age (7 males, 67±3.2 years) in whom arterial hypertension and any cardiovascular disease were excluded, based on a thorough clinical and laboratory examination.

MEASUREMENTS

A neurological evaluation which included a detailed medical history and structured physical examination was performed to all the subjects enrolled in this study, with a neurologist unaware of the patient condition.

LABORATORY TESTS INCLUDED

Cerebral Magnetic Resonance Imaging (MRI) was performed on a 1.5 T imager Philips Gyroscan. Images were obtained by using the next sequences:

1. Sagittal and coronal T1-weighted TR: 500; TE: 15; THK: 6 mm; Gap 1.0; Matrix 179 x 256; FOV: 250; Scan Time: 2:35 min; NSA 2.
2. Axial Fluid Attenuated Inversion-Recovery (FLAIR) TR: 8000; TE: 180; TI: 1900; THK: 5 mm; GAP 1.0; Matrix: 245 x 256; FOV 230; Scan Time: 4:00.
3. T2-weighted axial, TR: 2700; TE: 30/90; THK: 6 mm; Matrix 179 x 256; FOV: 230; TSCAN: 8:09 min.

Periventricular white matter lesions on T2 images were classified as previously reported by Longstreth jr *et al.* [17], using a 0 to 9 scale with 0 for normal and 9 for the most severe WML as:

- *Grade 1:* discontinuous periventricular rim or minimal dots of subcortical disease white matter;
- *Grade 2:* thin, continuous periventricular rim or few patches of subcortical WMLs;
- *Grade 3:* thicker continuous periventricular rim with scattered patches of subcortical WMLs;
- *Grade 4:* thicker shaggier periventricular rim and mild subcortical WMLs that may have minimal confluent periventricular lesions;
- *Grade 5:* mild periventricular confluence surrounding the frontal and occipital horns;
- *Grade 6:* moderate periventricular confluence surrounding the frontal and occipital horns;
- *Grade 7:* periventricular confluence with moderate involvement of the Centrum Semiovale and;
- *Grade 8:* periventricular confluence involving most of the Centrum Semiovale,
- *Grade 9:* presence of lesions affecting the whole white matter.

Cerebral MRI classification was performed by a neuro-radiologist blinded of the clinical status of the subjects under evaluation. Patients with cerebral lacunae were not included in this study.

BLOOD PRESSURE MEASUREMENTS

Ambulatory Blood Pressure Monitoring (ABPM)

It was carried-out on a working day by an automated portable recorder (Spacelab 90207; Richmond, California; USA). With the cuff wrapped around the non-dominant arm, measurements were performed every 15 minutes during the day-time period (from 6 AM to 10 PM) and every 20 minutes during the night-time period (10 PM to 6 AM). During the recording, patients were instructed to attend their usual activities, to fill a diary specifying the time to bed and the time of awakening together with the meals time and the time of the most relevant activities. They were also instructed to refrain from unusual physical exercise and to keep the instrumented arm still at the time of each blood pressure measurement.

For each recording hour over the whole 24 hour period, and over the daytime and the night-time sub-periods, average systolic, diastolic, pulse pressure and heart rate values together with their respective standard deviations, were separately calculated.

Beat to Beat finger Blood Pressure Monitoring

It was performed by a Finapres Device (Finapres, Ohmeda Colorado, USA). The digital cuff was wrapped around the 2^{nd} phalanx of the middle or ring finger of the non-dominant arm. The recordings were carried-out during 2 hours. During the first hour the patient lay supine in a quiet room. During the second hour, under continuous finger BP recording, the patient was randomly assigned to perform four laboratory manoeuvres:

1. Isometric hand-grip exercise: at 60% of their maximal strength for 90 sec, followed by a recovery phase of 13.5 min.
2. Cold Pressor test: by hand immersion into iced water for 60 sec, followed by a 14 min recovery period.
3. Relaxing activities: watching TV, chatting with relatives and friends, or reading a book or a newspaper over the 15 min.
4. Active standing: after the first one hour period, the patient was asked to stand up and stay in the upright position for fifteen minutes.

The blood pressure signal registered through the Finapres was online sampled at 100Hz, A/D converted (National Inst.) and stored on an IBM PC compatible computer. The digitized signal was edited from artefacts by an interactive procedure and subdivided into separate pulse waves from which the systolic (SBP) and diastolic blood pressure (DBP) were computed and the mean blood pressure (MBP) calculated as the integral of the BP waveform. The pulse interval (PI) was derived from the blood pressure signal as the time interval between consecutive systolic peaks. The calculated SBP, DBP, MBP, PP and PI parameters were stored into separate time series for further analysis. The BP and PI data were averaged over the one hour supine recording period. The respective standard deviations or variances were taken as measures of the corresponding overall blood pressure and pulse interval variability. For each laboratory manoeuvres, during the 15 min test performance, average BP and PI values were computed for the three sub-periods of 5 min each. The BP and PI response to each test considered was the maximal change during the test as compared to the average BP or PI value of the one hour supine recording period and to the average value of the last 5 min of the respective recovery period.

During the one hour supine recording period and during each of the three 5 min sub periods of the 15 min test performance, spontaneous baroreflex sensitivity (BRS) was also computed. This was done both in the time domain, by the sequence method, and in the frequency domain, by calculation of the alpha coefficient. The former method is based on the computer identification over the recording period of the spontaneously occurring sequences of consecutive heart beats characterised by either a progressive increase in SBP and lengthening in pulse interval (PI, the reciprocal of heart rate) or by a progressive reduction in SBP and shortening in PI [18].

The slope of the regression line between linearly related changes in SBP and PI over these sequences is taken as an index of the sensitivity of the baroreceptor-heart rate reflex, as done with the technique based on iv injection of vasoactive drugs [18]. BRS was also assessed in the frequency domain by computing the squared ratio between PI and SBP powers in those frequency regions where the fluctuations in these signals are coherent (coherence > 0.5). This occurs at the respiratory frequency (High Frequency, alpha HF, 0.15-0.4 Hz) and at the frequency of the so-called Mayer waves (Low Frequency, alpha LF, 0.04-0.15 Hz).

For each study condition, individual data were calculated for normotensive and hypertensive subjects, and were then averaged for the respective group.

NEUROPSYCHOLOGICAL ASSESSMENT

The patients were evaluated by the following tests:

1. Mini-mental test
2. Weschler Adult Intelligence Scale (WAIS). Includes tests of information and analogies, digit span, digit symbol and vocabulary.
3. Attention
4. Verbal memory: Rey Auditory Verbal Learning Test (RAVLT), to evaluates immediate memory, learning, interference factors and recognition.
5. Visual memory: Rey-Osterrieth Complex Figure Tests, to evaluate visual memory.
6. Language: Boston Naming Test.
7. Executive Function: to evaluate the frontal lobe with tests of attention, flexibility mental: Trail Making test B; Oral

Controlled Word Association test that evaluates the verbal fluency.

8. Geriatric Depression Scale (G.D.S):

- Normal old men: 0-10 points
- Depression of progressive graveness: 11 points or more

For elderly subjects with serious depression the score was 23±5.

Clinical Dementia Rating (CDR)

Clinical staging instrument for dementia that characterizes six domains of cognitive and functional performance: memory, orientation, judgment &problem solving, community affairs, home & hobbies, and personal care. In addition to ratings on a 5-point scale for each domain (except Personal Care, which is rated on a 4-point scale) an overall CDR score is derived by standard algorithm (http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html). This score is useful for globally staging the level of impairment: 0 = No impairment, 0.5, 1, 2, and 3 indicate Very Mild, Mild, Moderate and Severe Dementia [19].

In our case, since the patients were older than 65years without neurological history, we were evaluating people in which a deficit associated with age and the starting of a deteriorative process was associated. This was a grey area in between 0 an 1 of the former classification. For this reason we reclassified them in:

0: patients without complaints and no cognitive impairment,

0-A: Patients with complaints without findings of cognitive impairment and

0-B: Patient with complaints and objective deficit.

The protocol was approved by the Ethical Committee of the Hospital and all the patients gave written informed consent before to be screened for inclusion in the study.

STATISTICAL ANALYSIS

All data are shown as mean ±SD.

The student's t test was used for comparison between sets of values. For the Correlation between BP parameters and WML the univariate Pearson correlation coefficients was used. Multiple regression analysis was also performed considering the Manolio index as the dependent variable always weighted by age with pressure levels, blood pressure SD as independent variables.

RESULTS

As shown in Table **1**, the NT and the HT groups were equivalent for age and BMI values. Hypertensive patients had office SBP values significantly higher than normotensive subjects, while, probably due to their age, office DBP was not different from the values of normotensive subjects. Conversely both SBP and DBP average daytime values were significantly higher in HT than in NT subjects. Hypertensive, hypertensive patients displayed a higher rate of WML.

Table 1. Demographic General Data

	Normotensive	Hypertensive	*P*
Age (years)	67.00 ±3.16	69.00 ±1.12	ns
BMI (Kg/m2)	27.61± 1.21	26.45± 2.03	ns
BP_{off} (mmHg)	125 ±5.4/ 79± 2	161±2.5/ 78±3	0.001/ns
BP_{dt} (mmHg)	126±5.5/ 76±4.3	150 ±2/85±1.5	0.001/0.02
WML (%)	16	60	0.03

It is shown the Age (years), Body Mass Index (BMI; Kg/m^2), and the Blood Pressure (BP (mmHg)) values registered in the office (BP off) and the day time (BP dt) mean values from the ABPM. White matter lesion was represented as percentage of appearance.

White matter lesions, showed a low but significant positive correlation with age (r=0.40; p<0.03; Table **2**). Following this observation, all subsequent correlations were weighted by age. WML displayed no correlation with DBP either in the office, over the 24h or when assessed beat-by-beat by Finapres. Conversely, a positive and significant correlation (Table **2**), even after accounting for the effects of age, was found between WML and SBP or PP, either when considering office, 24h, day time or night time mean values.

Table 2. Office and ABPM Mean Blood Pressure Values and Their Correlation with White Matter Lesions

	Mean	r	*P=*
Age (years)	69 ±1.1	0.395	0.034
SBP_{off} (mmHg)	161.3 ±2.5	0.435	0.034
PP_{off} (mmHg)	78.4 ±2.9	0.47	0.021
SBP_{24h} (mmHg)	143.4± 2.1	0.411	0.05
PP_{24h} (mmHg)	65.6 ± 3.1	0.621	0.003
SBP_{dt} (mmHg)	150.3 ± 2	0.35	0.05
PP_{dt} (mmHg)	68.6 ±4.3	0.485	0.05
SBP_{nt} (mmHg)	133.3 ±3.1	0.768	0.030
PP_{nt} (mmHg)	59.4 ±4.3	0.945	0.0004

It is shown the age (years) and the office (off) and the twenty four hours (24h), day time (dt), and night time (nt) systolic and pulse pressure mean values (mmHg). R= correlation coefficient and p= statistical value.

WML failed to show any correlation with SBP average values derived from the Finapres recordings either in the supine or in the upright position (Table **3**), while it was positively and significantly related to PP in both conditions. In a similar way, beat-to beat SBP variability, either in the supine or in the upright position, showed a positive and significant correlation with WML (Table **3**).

Laboratory Manoeuvres

For all the three laboratory manoeuvres involving a sympathetic activation, i.e. Standing-up, Hand-Grip and Cold Pressor test, SBP and DBP final values reached were significantly higher in HT than in NT (Fig. **1**). Similarly, SBP, DBP or MBP variability were significantly higher in hypertensive subjects under either laboratory instrumentation when compared with the resting period (Fig. **2**).

Table 3. Correlation Between WML and Finapres Values During Maneuvers

	Mean	r	*P*
SBP_{fin} Sup (mmHg)	149.4 ±5.6	0.281	Ns
PP_{fin} Sup (mmHg)	72 ± 3.9	0.617	0.001
SBP_{fin} St-up (mmHg)	171.2±6.2	0.274	ns
PP_{fin} St-up (mmHg)	75.2±4.7	0.615	0.001
Var SBP_{fin} St-up (mmHg)	14.5± 2.1	0.591	0.01
Var SBP_{fin} St-up (mmHg)	11±0.8	0.456	0.03

It is shown the systolic and diastolic (SBP and DBP; mmHg) mean values and the blood pressure variability (Var; mmHg) in the supine (Sup) and the stand-up (St-up) conditions. R= correlation coefficient, p= statistical value.

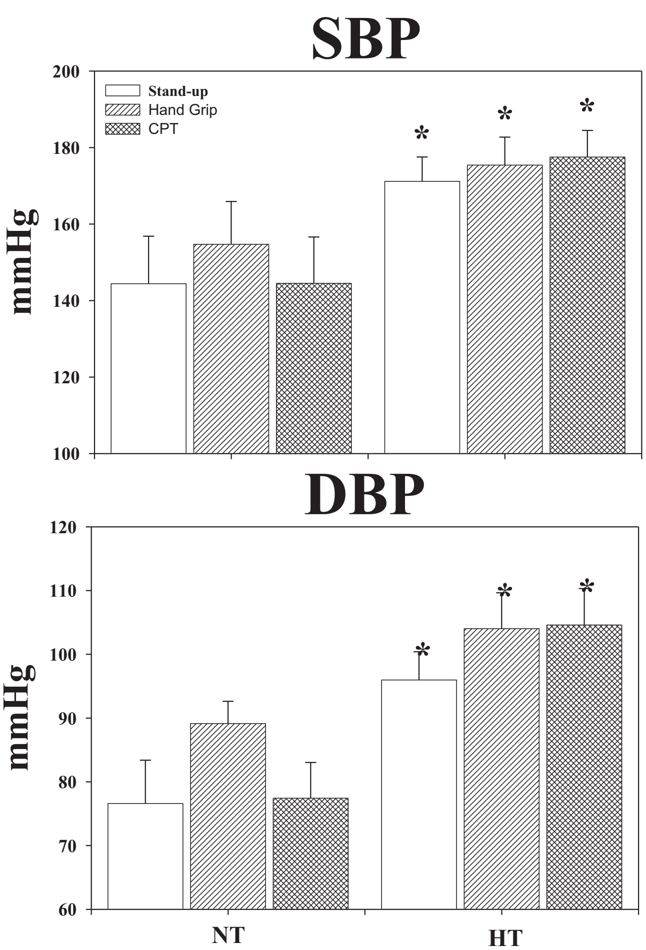

Fig. (1). Blood Pressure response to sympathetic activating manoeuvres. It is shown the systolic (SBP) and diastolic (DBP) blood pressure responses to stand-up (open columns), handgrip (Stripped column) and cold pressor test (CPT; squared columns) manoeuvres observed in normotensive (NT) and hypertensive (HT) subjects. p<0.05 when compared to the respective NT value.

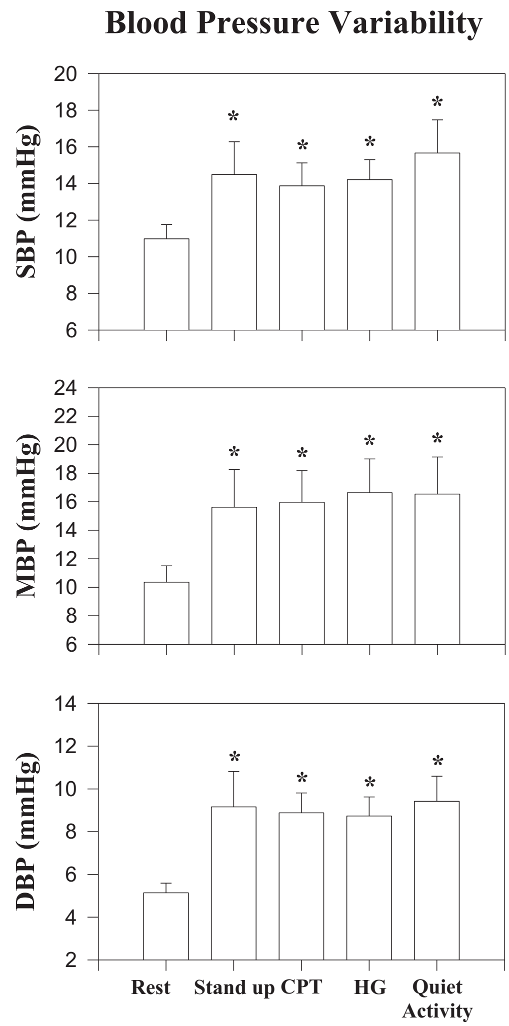

Fig. (2). Blood pressure variability response in hypertensive subjects to sympathetic activating manoeuvres. It is shown the responses in systolic (SBP), mean (MBP) and diastolic (DBP) blood pressure from by the beat to beat BP recording during recumbent and after manoeuvres.

During the resting period (Table **4**), BRS, when calculated through the sequence method (Time Domain) was similar in HT and NT subjects, when pooling together hypertension-bradycardia and hypotension-tachycardia sequences. However when BRS was assessed in the frequency domain by the alpha LF and the alpha HF coefficients, a significant reduction was observed in HT compared with NT.

At the time of laboratory manoeuvres implying sympathetic activation, BRS as assessed in the frequency domain was significantly reduced as compared to the resting values (Fig. **3**) being particularly evident for the alpha HF values (Table **4**).

Neuropsychological Assessment

Comparing HT and NT subjects and their correlation with abnormal Manolio, only the evaluation of semantic

Table 4. Mean Blood Pressure and Baroreflex Sensitivity

	Rest	
	HT	**NT**
MAP (mmHg)	99.93±4.36	85.70± 4.81*
BRS (msec/mmHg)	8.1±1.0	8.31±0.90
Alfa MF($msec^2/mmHg^2$)	3.7±0.4	5.67±0.50*
Alfa HF($msec^2/mmHg^2$)	7.1±0.9	10.36±1.17 **

It is shown the mean arterial pressure (MAP), The baroreflex sensititivity (BRS) and the power spectral calculated baroreflex sensitivity (Alpha; $msec^2/mmHg^2$) in the medium (LF) and the higher (HF) frequency oscillatory windows. *p<0.001, ** p=0.034.

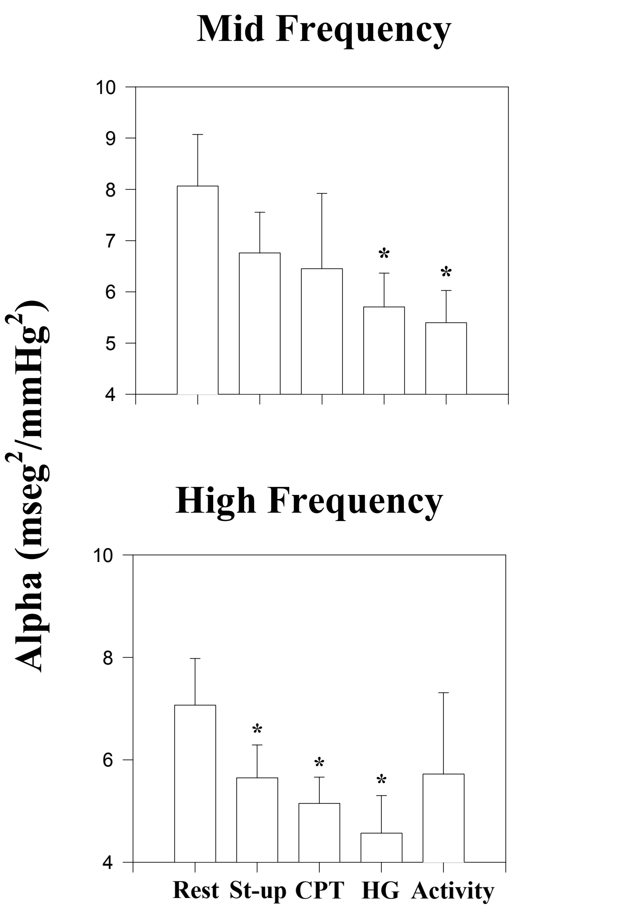

Fig. (3). Frequency domain baroreflex activity (Alpha). It is shown the sympathetic (Low Frequency) and parasympathetic (High Frequency) components of the baroreflex sensitivity under the sympathetic activating manoeuvers (reference see Fig. **1**) compared to their respective values in resting position (Rest=recumbent). *= p< 0.025.

fluency was statistically significantly (p=0.011). When analyzing the RVLT results in patient divided in older or younger than 75 years (Fig. **4**), a significant difference was observed in the delayed analysis of words, and in the phonological fluency (p<0.04). In these patients, a bigger rate of pathological results in the delayed recovery test was observed in subjects older than 75 years (28%) compared with the younger group (5%).

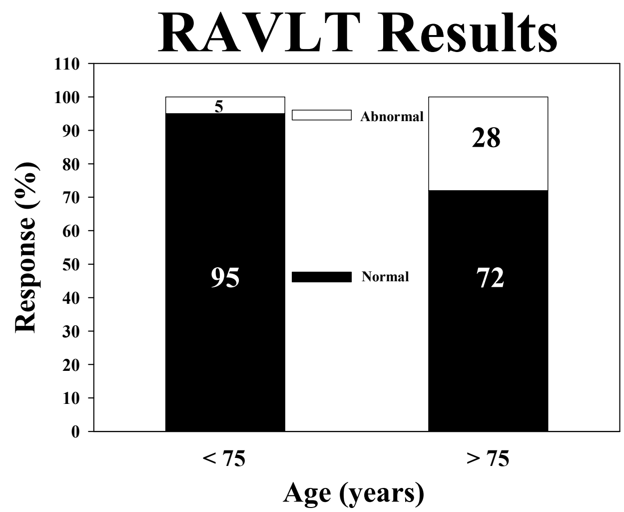

Fig. (4). It is shown the percentage in normal (open column) and abnormal (closed column) responses obtained in patients younger (<75) or older (>75) than 75 years.

DISCUSSION

Brain magnetic resonance imaging, can visualise two different types of lesions related to hypertensive cerebrovascular disease: the lacunae and the periventricular white matter abnormalities. Lacunae are small, deep infarcts from penetrating arteriolar occlusive disease able to produce characteristic lacunar-stroke syndromes, while periventricular white matter lesions, attributed to rarefaction of the myelin sheath, are frequently incidental findings seen in the elderly. Furthermore the periventricular white matter is considered to be an arterial border zone, in terms of the vascularization pattern, thus susceptible to low flow ischemia [20, 21] ([1]9,20) and the occurrence of the typical ischemic lesions.

The major finding of this study was a closer correlation of WML with ABPM than with office BP that was also observed with other target-organs, as cardiac hypertrophy and retinopathy [22]. In addition, there was a strong correlation between WML and the nocturnal period of ambulatory BP monitoring compared with the awake and the total 24 hour-periods. In these patients we have also found that autonomic system, through the vagal component of the baroreflex system, was impaired.

Different patterns of diurnal-nocturnal ABPM have been reported in elderly patients with essential hypertension. Toghi *et al.* [23] described it in half of their hypertensive patients with lacunar infarcts and Binswanger type of dementia. Furthermore, Kario *et al.* [24], found a relationship between extreme dipping and silent cerebrovascular damage while Yamamoto *et al.* [25] have considered that multiple lacunar lesions might play an important role in causing reduced nocturnal blood pressure dipping, whereas periventricular white matter intensities do not relate to nocturnal blood pressure dipping. Conversely, Chamorro *et al*. [26, 27] suggested that both types of radiological lesions, react to separate hemodynamic mechanisms, where silent lacunar infarcts seem to be related to elevate diurnal BP while white matter periventricular lesions could be associated to a reduced nocturnal BP dipping. Our findings showed a strong relationship of WML with nocturnal SBP and nocturnal pulse pressure in the two BP readings, beat to beat (Finapres) analysis and ABPM.

Blood pressure variability was significantly higher in hypertensive patients than in normotensives. In this regard, Fluckier *et al.* [28] evaluated the relationship between age and short term heart rate and blood pressure variability. They found, in normotensive subjects, that the effect of aging was progressive and continuous throughout the 18th to 80th years old range. Regarding the spectral analysis evaluation, a continuous and linear reduction of the heart rate low frequency oscillations, related to age in standing position, and in high frequency was also observed. Although the authors have not found any correlation between age and BP variability, they have shown a negative correlation between age and the absolute LF power of diastolic BP variability, during upright position. However, in our study we have found that the sympathetic activity, during the stress maneuvers, was preserved whereas the vagal component was deteriorated. This is coincidental with the above mentioned data and supports the idea that, in older subjects, a reduced parasympathetic activity is present. This is further supported by the observation that the BRS high frequency band, which represents the vagal activity, was significantly reduced. However, we must take into account that aging is also associated with a depression of the renin angiotensin system, a reduction in vascular compliance and endothelial dependent vasodilatation and to an increase in vascular peripheral resistance. Each one of them may contribute to the decrease activity in the LF baroreflex band [29].

Aging is related with an impaired memory function [14] and the majority of elderly individuals aged over 65 years frequently have memory related complaints. However, the memory fragility in the elderly has shown to be extremely variable [30]. In our work, we failed to find any significance in the neurocognitive performance, when comparing hypertensives with white matter lesions and normotensives. In this regard it is important to mention that verbal fluidity (VF) requires evocation in a limited period of time (usually 1 min.) with a specific category of words. This test could be phonologic and/or categorical or semantic. Each one of these evaluations may involve different cognitive processes related to attention, semantic memory and speed for information processing, cognitive flexibility and work memory [31]. Among the tests examined, the verbal fluency involves many linguistic aspects and may be less reliable. On the other hand, the test of fluency categorical (semantics) has been shown to be more specific for evaluating neurocognitive impairment in the elderly [32]. In our study, when verbal memory was analyzed in individuals aged higher or lower than 75 years a significant lower performance was observed in the older group in the deferred recovery task. Thus, and in accordance with Mangone *et al*. [33], the age related alterations observed in episodic memory is attributable to a reduced efficiency to initiate the optimal operations for the codification and recovery of the requested information. This could represent an ageing effect rather than a blood pressure related consequence.

Finally, our results are in agreement with van Boxtel *et al*. [34] in which an absence of association among dipping BP status, white matter lesions and cognitive deterioration was found. The reason of the disagreement between our results and van Boxtel *et al*. with other studies [35] might be related to our smaller population studied or the brain distribution of the white matter lesions.

In conclusion, night-time ambulatory blood pressure monitoring and SBP variability, in upright position, are the best predictors of silent cerebral WML. The autonomic nervous system might be involved in the pathogenesis of these lesions, since the vagal component is reduced. This could also explain the depressed baroreflex sensitivity accompanying the ageing process.

Neurocognitive alterations in the elderly have a multifactorial origin, in which the ageing process seems to be the principal component.

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