Acta Neurologica Belgica
https://doi.org/10.1007/s13760-021-01664-8

ORIGINAL ARTICLE

The circadian rhythm of arterial blood pressure in Alzheimer's disease and vascular dementia

Matei Daniela[1] · Carmen Grigoras[1,3] · Dan Cuciureanu[2] · Victor Constantinescu[2]

Received: 6 November 2020 / Accepted: 26 March 2021

Abstract
Hypertension is considered a risk factor for stroke and dementia. Ambulatory blood pressure monitoring (ABPM) is a useful tool in the diagnosis and treatment of hypertension. This study aimed to evaluate blood pressure using ABPM, in 30 Alzheimer's disease (AD) patients and 30 vascular dementia (VaD) patients in comparison with 30 healthy controls. BP was recorded every 15 min from 6 AM to 10 PM, and every 30 min from 10 PM to 6 AM. Mean systolic (SBP) and diastolic (DBP) blood pressure during daytime, nighttime, diurnal index, pulse pressure, and heart rate were extracted from the ABPM recordings. VaD patients presented higher SBP values compared to AD patients and healthy controls. DBP values in the AD group were the lowest, while VaD patients presented the highest DBP values, including day and nighttime. Mean arterial pressure values were also the highest in the VaD group, while AD patients had similar values with the control group. The VaD patients presented the lowest systolic diurnal index compared to AD patients and controls. The mean pulse pressure and nighttime pulse pressure values were higher in both groups of dementia patients when compared with the control group. Increased SBP, pulse pressure, and alteration in the circadian pattern with the highest incidence of the non-dipper and reverse dipper patterns were found in patients with dementia when compared with the healthy elderly. Also, decreased values of DBP were found in AD patients, especially during the night period.

Keywords Vascular dementia · Hypertension · Alzheimer's disease · Ambulatory blood pressure monitoring

Introduction

Hypertension is a risk factor for cardiovascular disease, stroke, and dementia. Increasing evidence shows that hypertension is involved in the pathogenesis of the most common forms of dementia, such as Alzheimer's disease (AD) and vascular dementia (VaD) [1]. The prevalence of hypertension in people with dementia varies between 35 and 84% [2–4].

High systolic blood pressure (SBP) in midlife increases the risk of dementia in the elderly [5, 6]. Not only high SBP values but also excessive fall in blood pressure (BP), including orthostatic and postprandial hypotension, contribute to cerebral damage (leukoaraiosis), which progresses to cognitive impairments [7–9]. A reduction in BP is observed several years before the diagnosis of AD and is considered by some researchers as an early change of the dementing process, which can be attributed to impaired cerebral autoregulation and endothelial dysfunctions [10, 11]. Recently, high pulse pressure or increased arterial stiffness was associated with damage to the endothelium and dementia [12, 13].

Ambulatory blood pressure monitoring (ABPM) for 24 h has become a useful tool in the diagnosis and treatment of hypertension, thus preventing future cardiovascular events.

This study aimed to describe BP characteristics in AD and VaD patients compared to healthy controls, using ABPM. We also searched for a correlation between the clinical, psychological, biochemical profile, and BP parameters.

✉ Carmen Grigoras
carmen.grigoras@umfiasi.ro

[1] Department of Biomedical Sciences, Faculty of Medical Bioengineering, University of Medicine and Pharmacy "Grigore T. Popa", 9-13 Kogalniceanu Street, 700454 Iasi, Romania

[2] Neurology Department, Faculty of Medicine, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania

[3] Institute of Computer Science of the Romanian Academy, Str. T. Codrescu nr.2, 700481 Iaşi, Romania

Published online: 27 May 2021

Methods

Participant recruitment and inclusion criteria

Sixty patients with diagnosed dementia (30 patients with AD and 30 patients with VaD) and 30 age-related normal subjects were evaluated in our study.

Diagnosis of AD was based on guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association guidelines (NINCDS-ADRDA) [14]. For diagnosed VaD patients, we used the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria and modified Ischemic Score of Hachinski (including imagistic-CT/MRI scan) [15, 16].

The inclusion criteria for the patients were the following: presence of cognitive impairment, neurological, imagistic, and psychiatric evaluation before the admittance in the study. The exclusion criteria were the presence of acute ischemic stroke or brain hemorrhage, white matter lesions due to non-vascular etiologies (e.g. multiple sclerosis), or major diagnosed psychiatric disorders. The inclusion criteria for the controls were: normal cognitive status, normal electrocardiograms, and no history of hypertension and diabetes mellitus (based on anterior BP and fasting blood sugar measurements).

The study protocol was approved by the local ethics committee. All subjects or caregivers of patients provided written informed consent before inclusion. The study was carried out in accordance with the Helsinki Declaration. Treatment adherence was carefully monitored by the caregivers.

Clinical, biochemical, psychological profile, and BP monitoring

A detailed medical history, clinical features, blood tests, and neuroimaging data were noted for all subjects included in the study. Also, height, weight, and body mass index (BMI), calculated as weight divided by height squared were measured.

Systolic and diastolic blood pressure (DBP) were measured in a supine position after ten minutes of rest, using an Omron MX blood pressure recorder, and every 60 s for 3 min in the upright position. Orthostatic hypotension was defined as a decrease in SBP of at least 20 mm Hg or in DBP of at least 10 mm Hg, within 3 min of standing [17]. Blood tests including total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, and fasting blood glucose were performed in all patients.

The assessment of the cognitive function was based on applying several scores. A score equal to or higher than 25 points for the Mini-Mental State Examination test (MMSE) was considered normal. A score lower than 25 points was considered an impairment of the cognitive status [18]. Frontal Assessment Battery (FAB) was used to discriminate between frontotemporal type dementia and AD (18 points are the maximum score, indicating no cognitive impairment) [19]. Also, the Geriatric Depression Scale (GDS) was applied, a score greater than 5 suggesting depression [20]. Instrumental Activities of Daily Living (IADL) scales reflect the patient's independence. IADL scores range from 9 to 27, as follows: less than 16 points indicate dependence, less than 26 points characterize partially dependent patients and 26–27 points indicate higher independent functioning in terms of daily activities [21].

ABPM was used for the evaluation of the circadian BP. This was recorded every 15 min from 6 AM to 10 PM, and every 30 min from 10 PM to 6 AM with an ABPM Holter device. The mean values of daytime and nighttime BP, diurnal index ([daytime SBP–nighttime SBP]/daytime SBP × 100) were calculated automatically. Also, pulse pressure, measured as differences between maximal SBP and DBP, and mean arterial pressure (MAP) calculated as [SBP + 2×DBP]/3 were calculated. According to the diurnal index, circadian BP variation could be subdivided into: dipping 10–20%, non-dipping < 10%, extreme dipping ≥ 20%, reverse dipping < 0% or nocturnal BP elevation [22, 23].

Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or both during the day, and SBP ≥ 125 mmHg or DBP ≥ 75 mmHg or both during the night period [22].

Statistical analysis

Data were analyzed using SPSS, version 4.0.1 (SPSS, USA), GraphPad Prism, version 8.2.1 (GraphPad Software, Inc. USA) and the Matlab software package. The results were expressed as mean ± standard deviation or as a percentage (%). Each variable was studied for significance in the discrimination among the three groups: VaD and AD patients and healthy controls. The normality of the distribution of variables was performed using the Shapiro–Wilk test. The nonparametric Kruskal–Wallis test, which does not rely on the assumption of normality, was used when the assumptions of ANOVA were not met in the analysis of the three groups. The significance was met when $p < 0.05$.

Sex-based segmentation of Smean, for each disease category, proved to be extracted from normally distributed populations, by means of the Shapiro–Wilk test ($p > 0.05$). Unbalanced two-factor ANOVA was performed followed, by post hoc analysis, Dunn–Sidak test, to determine the source of variation, for the observed significant differences among groups of disease category, providing a source of variation between VaD and AD categories, for sex = M. Performing

Shapiro–Wilk and Levene tests, only two of the variables considered for this analysis proved to meet the conditions for ANOVA test application. For the other variables, Scheirer–Ray–Hare extension of the Kruskal–Wallis test, adequate for two factors design, was performed along with two-factor ANOVA. The post hoc analysis was performed by means of both Tukey–Kramer and Dunn–Sidak methods. Probabilities less than 0.05 means 'significant differences' between the population's distribution characteristics for the analyzed samples. The post hoc analysis attests to the cause of variation for ANOVA and/or Kruskal–Wallis test results stating such variations.

Results

We included in our study 30 AD patients (18 women, 12 men; mean age 75.33 ± 4.71 years), 30 VaD patients (13 women, 17 men; mean age 73.70 ± 3.90 years), and 30 normal subjects (15 women and 15 men; mean age 75.10 ± 5.07 years). The groups did not differ by age and gender. BMI was increased in VaD patients 27.3 ± 2.4 kg/m^2 compared with AD 24.7 ± 2.5 kg/m^2 ($p < 0.05$) (Table 1).

The incidence of hypertension was higher in VaD groups compared to the AD group [VaD—23 patients (76.6%) vs AD—16 patients (53.3%)]. Also, the diabetes mellitus was more common in the VaD group (12 patients—40%) compared to the AD group (9 patients—30%). The VaD group had higher levels of blood glucose, total cholesterol, triglycerides, and lower values of HDL-cholesterol compared to AD and controls (Table 1).

Cognitive tests revealed differences between the three groups. VaD and AD patients had lower MMSE, FAB, GDS, IADL scores compared to controls. The lowest FAB score was found in VaD patients and the lowest IADL score was found in the AD group (Table 1).

Eleven patients received angiotensin-converting enzyme (ACE) inhibitors, 7 patients received angiotensin II receptor blockers (ARB) and 21 patients received a combination of antihypertensive drugs (ACE inhibitors, beta-blockers and diuretics). Seven AD patients received Donepezil (Aricept®), and 21 patients were under oral antidiabetic.

VaD patients presented higher SBP values compared to AD patients and healthy controls. There was no significant difference between AD patients and the control group (Table 2). VaD patients presented higher values for daytime and nighttime SBP compared to the other two groups, while the AD patients presented the lowest diurnal SBP values (Table 2).

DBP values in the AD group were the lowest, while VaD patients presented the highest DBP values, including day and nighttime (Table 2). MAP values were also the highest in the VaD group, including daytime and nighttime values, while AD patients had similar values with the control group. The VaD patients presented the lowest systolic diurnal index compared to AD patients and controls (Table 2).

The mean pulse pressure and nighttime pulse pressure values were higher in both groups of dementia patients when

Table 1 Clinical and biochemical features of the groups

Parameter	VaD $N=30$	AD $N=30$	Control $N=30$
Age (years)	73.70 ± 3.90	75.33 ± 4.71	75.10 ± 5.07
Sex M/F	17/13	12/18	15/15
BMI (kg/m^2)	27.3 ± 2.4**	24.7 ± 2.5	25.7 ± 2.4•
MMSE score	22.06 ± 1.99**	18.6 ± 2.92††	28.52 ± 1.54••
FAB total score	9.5 ± 1.85*	12.6 ± 1.2†	17.4 ± 1.15••
GDS score (short)	4.3 ± 3.28	4.1 ± 2.2†	2.45 ± 2.1•
IADL score	8.83 ± 2.37**	7.1 ± 1.58††	26.25 ± 0.85••
Fasting blood sugar (mg/dl)	112.4 ± 14.4*	104.4 ± 17.8	102.3 ± 13.25•
Total cholesterol (mg/dl)	194.1 ± 44.7*	151.2 ± 49.7†	176.3 ± 22.3
HDL-cholesterol (mg/dl)	39.5 ± 2.84	43.5 ± 3.4	46.82 ± 2.65•
Triglyceride (mg/dl)	169.5 ± 54.1*	124 ± 42.8	128.5 ± 45.06
Uric acid (mg/dl)	5.4 ± 1.76	4.26 ± 1.436	3.21 ± 1.45•
Creatinine (mg/dl)	1.1 ± 0.45	0.96 ± 0.34	0.98 ± 0.46

Data: expressed as means ± standard deviation

BMI body mass index, *MMSE* mini-mental status examination, *GDS* geriatric depression scale, *IADL* instrumental activity of daily living

* $p < 0.05$; ** $p < 0.01$ when comparing VaD with AD groups

† $p < 0.05$; †† $p < 0.01$ when comparing AD with C groups

• $p < 0.05$; •• $p < 0.01$ when comparing VaD with C groups

Table 2 Blood pressure and heart rate characteristics in the three groups

Parameter	VaD patients $N=30$	AD patients $N=30$	Control group $N=30$	p value		
				VaD-AD	VaD-C	AD-C
SBP mean	131.60 ± 13.83	120.40 ± 16.82	123.20 ± 10.01	0.0061	0.0111	0.2402
SBP max	163.40 ± 25.30	147.0 ± 19.18	154.40 ± 12.39	0.0153	0.1736	0.1329
SBP min	108.70 ± 13.40	96.40 ± 16.05	97.70 ± 10.78	0.0025	0.0016	0.4242
SBP day	135.0 ± 14.81	121.80 ± 14.45	128.13 ± 10.89	0.0012	0.0616	0.0218
SBP night	128.06 ± 14.55	119.09 ± 20.84	118.25 ± 9.67	0.0442	0.0061	0.6464
S-DI	2.74 ± 9.87	5.0 ± 6.72	8.61 ± 4.02	0.4783	0.0213	0.0027
DBP mean	77.57 ± 11.06	70.18 ± 11.69	75.49 ± 9.53	0.0166	0.6783	0.0222
DBP max	104.40 ± 15.19	92.77 ± 15.38	96.87 ± 11.54	0.0025	0.0623	0.0551
DBP min	55.93 ± 10.45	48.78 ± 11.85	55.40 ± 9.35	0.0462	0.9093	0.0504
DBP day	81.23 ± 11.98	73.68 ± 15.02	79.32 ± 10.13	0.088	0.5642	0.0934
DBP night	73.91 ± 11.51	66.69 ± 10.91	71.66 ± 9.43	0.0465	0.7108	0.0692
MAP mean	96.72 ± 11.37	86.79 ± 10.54	91.12 ± 9.36	0.0039	0.0418	0.1098
MAP max	121.74 ± 15.65	108.23 ± 12.28	112.77 ± 12.53	0.0005	0.0126	0.1388
MAP min	74.97 ± 10.78	67.47 ± 10.46	71.50 ± 9.34	0.0113	0.1785	0.1273
MAP day	100.32 ± 12.19	90.39 ± 13.24	95.48 ± 10.05	0.0020	0.2037	0.0222
MAP night	93.11 ± 12.03	83.19 ± 14.70	86.76 ± 9.08	0.0163	0.1065	0.2647
PP mean	57.45 ± 12.58	54.73 ± 12.26	48.52 ± 8.07	0.3560	0.0056	0.0585
PP max	78.07 ± 16.16	73.93 ± 15.73	68.50 ± 12.74	0.2975	0.027	0.3186
PP min	34.27 ± 9.19	32.17 ± 7.80	31.27 ± 7.0	0.5935	0.3215	0.5938
PP day	53.82 ± 12.0	51.11 ± 10.90	48.76 ± 9.39	0.5109	0.1493	0.4875
PP night	54.14 ± 11.59	54.03 ± 14.65	46.49 ± 8.88	0.6623	0.0129	0.0790
HR mean	79.57 ± 8.98	78.98 ± 10.16	71.20 ± 8.20	0.7551	0.0002	0.0012
HR max	108.73 ± 27.76	107.60 ± 23.56	110.40 ± 30.18	0.8687	0.8283	0.9327
HR min	59.60 ± 9.52	60.70 ± 7.56	57.93 ± 9.05	0.5149	0.5391	0.1249
HR day	85.42 ± 9.43	85.45 ± 11.59	84.08 ± 11.67	0.8516	0.4295	0.6946
HR night	73.73 ± 9.70	72.64 ± 10.2	61.22 ± 10.14	0.5945	0.0001	0.0001

SBP systolic blood pressure (mmHg), *DBP* diastolic blood pressure (mmHg), *MAP* mean arterial pressure (mmHg), *PP* pulse pressure (mmHg), *HR* heart rate, *b/min* beats/min, *AD* Alzheimer's disease, *VaD* vascular dementia; Statistical significance when $p < 0.05$

compared with the control group. There was no significant difference between the two groups of patients in this respect. VaD patients presented the highest pulse pressure values in the three groups (Table 2). Mean heart rate (HR) and nighttime HR were increased in AD and VaD patients compared to controls, while diurnal HR displayed no significant differences between the three groups.

Adding a supplementary factor, sex, to the analysis, the volumes of the groups decrease and the power of the test is diminished accordingly. The results are shown in Table 3. The first columns in Table 3 include the 95% confidence intervals for means for both females and males, for the three disease groups: control, VaD, and AD. The variables which emphasize significant differences between groups remain SBP mean and day time, with $p < 0.002$, MAP mean and pulse pressure mean with $p \leq 0.02$, the source of variation being mostly between VaD and AD disease groups for both males and females, only for pulse pressure mean the source of variation lies between VaD and Control groups. Figure 1 presents comparative box plots for each variable included in Tables 3, for the 3 disease categories: VaD, AD, and Control, which had shown to be discriminative for the disease, for each of the two sexes. Figure 2 presents the 3D interpolation of the points determined by the three coordinates, SBP mean, SBP day, and MAP mean, for the 2 sexes, F and M, for each disease condition: Control, VaD, and AD. This thin plate spline interpolation can serve as a disease predictor for the population from which the samples were extracted, the spline regression surfaces being distinct for each condition.

Comparative classification results of both interpolation-based classification and set-based classification, using different classification algorithms, such as kernel support vector machine (SVM), subspace discrimination and k-nearest neighbors (KNN), and linear principal component analysis (PCA) preprocessing are presented in Table 4, where the classification performances were evaluated through overall accuracy. SVM-based classification of the preprocessed sets provided the best results. Their

Table 3 Holter parameters compare by sex and disease

	F			M			ANOVA				F	M	M	F vs. M	
	Control	VaD	AD	Control	VaD	AD	Sex	Disease	Sex and disease	Kruskal–Wallis	Post hoc VaD vs. AD	Post hoc Control vs. VaD	Post hoc VaD vs. AD	Post hoc VaD vs. AD	Post hoc VaD vs. Control
SBP-mean	125.38 ± 7.89	133.15 ± 8.93	121.05 ± 8.54	127.09 ± 6.41	136.24 ± 7.05	118.7 ± 11.28	0.80	0.0013	0.77		0.24	0.5193	0.03	0.04	0.9933
S-DI	9.81 ± 1.84	7.26 ± 5.49	1.86 ± 5.88	7.45 ± 2.32	6.49 ± 3.72	7.1 ± 2.14	0.66	0.11	0.13	0.19					
SBPday	131.85 ± 8.27	137.9 ± 6.45	121.92 ± 6.6	132.03 ± 6.61	141.03 ± 7.99	122.9 ± 10.92	0.63	0.00007	0.92		0.02	0.4663	0.012	0	0.9906
SBPnight	118.91 ± 7.70	128.3 ± 12.0	120.1 ± 11.38	122.15 ± 6.61	131.45 ± 7.24	114.5 ± 11.74	0.95	0.02	0.54	0.10	0.78	0.6055	0.111	0.36	0.9932
DBP-mean	75.55 ± 5.45	78.3 ± 6.68	68.8 ± 3.39	77.23 ± 6.83	75.58 ± 4.75	70.32 ± 11.37	0.95	0.02	0.70	0.12	0.20	0.9984	0.798	0.32	0.9999
DBPday	81.20 ± 5.84	82.25 ± 6.56	71.81 ± 3.94	80.97 ± 6.6	80.86 ± 5.68	75.2 ± 14.28	0.83	0.03	0.76	0.03	0.11	0.9999	0.433	0.16	0.4325
DBP-night	69.90 ± 5.31	74.34 ± 8.24	65.78 ± 4.15	73.49 ± 7.19	70.29 ± 4.53	65.44 ± 10.05	0.91	0.05	0.44	0.36					
MAP-mean	86.47 ± 14.08	96.58 ± 6.83	86.24 ± 4.52	93.42 ± 6.92	95.8 ± 4.77	76.87 ± 17.45	0.77	0.01	0.18	0.02	0.18	0.9972	0.042	0.05	0.9999
PPmean	49.29 ± 7.09	54.86 ± 6.62	56.72 ± 6.42	48.96 ± 3.36	60.66 ± 6.31	53.61 ± 7.51	0.75	0.01	0.32	0.06	0.99	0.0547	0.579	0.91	0.7417
PPday	50.65 ± 7.94	55.67 ± 7.52	50.11 ± 5.55	51.06 ± 3.92	60.17 ± 6.11	47.75 ± 18.99	0.79	0.07	0.69	0.12					
PPnight	49.01 ± 6.94	54.05 ± 6.16	54.4 ± 9.02	48.66 ± 4.04	61.16 ± 6.79	49.07 ± 11.79	0.87	0.05	0.24	0.06					
HRmean	72.89 ± 10.18	75.04 ± 8.18	68.97 ± 4.67	71.41 ± 4.19	69.04 ± 4.89	68.38 ± 9.36	0.31	0.48	0.67	0.69					

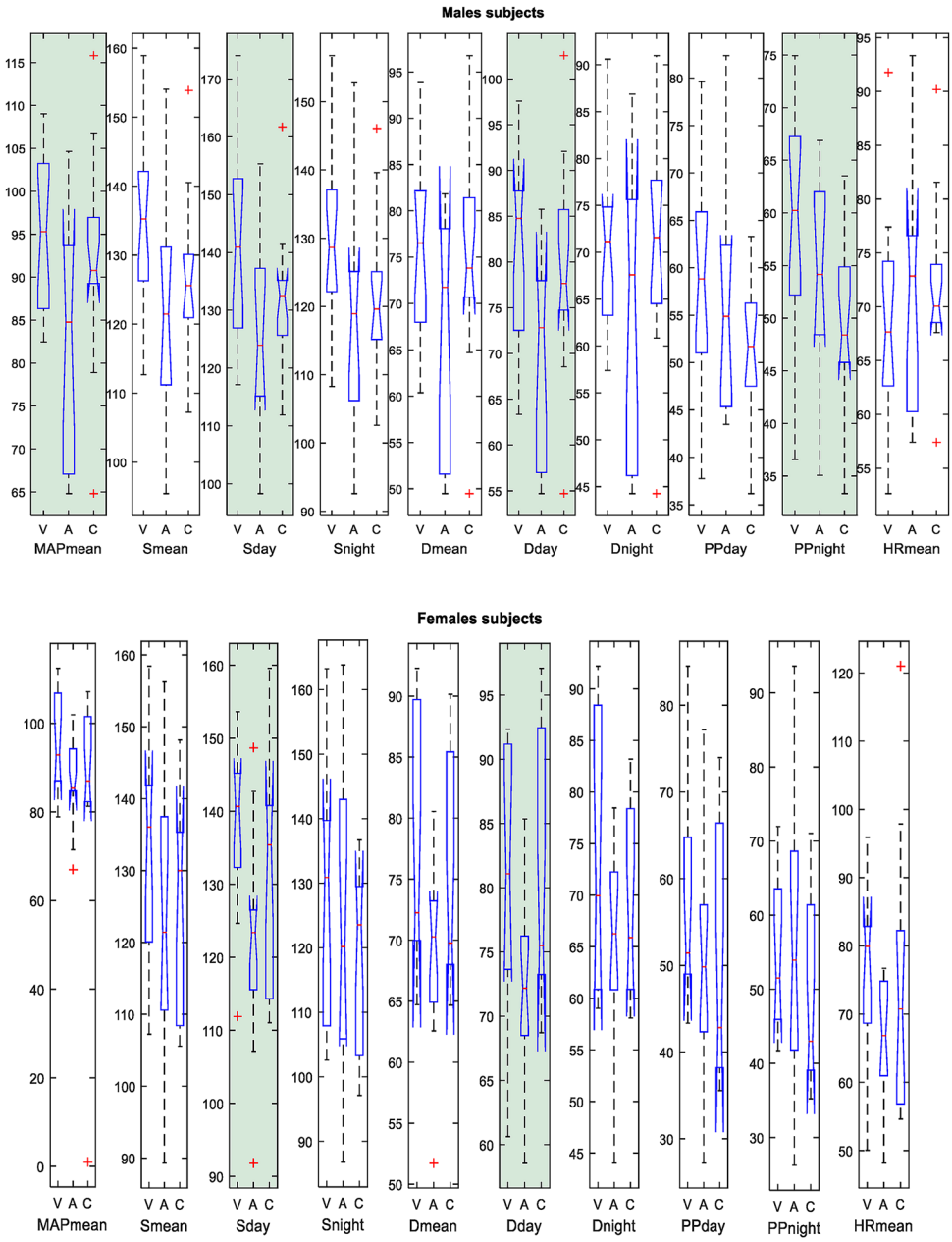

Fig. 1 Comparative boxplot representation of the most significant variables for the discrimination of VaD, AD and Control groups simultaneously. S = SBP: systolic blood pressure (mmHg), D = DBP: diastolic blood pressure (mmHg), MAP: mean arterial pressure (mmHg), PP: pulse pressure (mmHg), HR: heart rate, b/min = beats/min, A = AD: Alzheimer's disease, V = VaD: vascular dementia, C = control group

low levels may be explained as due to the small volumes of the groups to be tested, but despite this, they have fair values and can serve as an argument to further deepen the research in this direction.

In terms of the BP pattern, 6 patients (20%) in VaD, 4 patients (13.3%) in the AD group were dippers vs 14 patients (46.6%) in the control group. Non-dipper profile was found in 16 patients (53.3%) in age-matched subjects, 18 patients (60%) in VaD and 15 patients (50%) in AD patients. An extreme dipping profile was found only in 6.6% VaD and AD patients. Reverse dipping was found in 4 (13.3%) patients with VaD and in 9 (30%) patients with AD. During the night period, DBP below 60 mmHg was found in 5 patients (16.6%) with VaD, in 7 patients (23.3%) with AD groups, and in 1 patient (3.3%) in the control group.

The Pearson correlation test, for a confidence interval of 95%, indicated a significant inverse correlation between MMSE and the GDS score ($r = -0.67$, $p < 0.0001$). We found a positive correlation between the SBP and BMI ($r = 0.41$, $p < 0.05$), mean pulse pressure, and triglycerides ($r = 0.37$, $p < 0.05$). Mean pulse pressure presented a negative correlation with the mean HR ($r = -0.60$, $p < 0.001$).

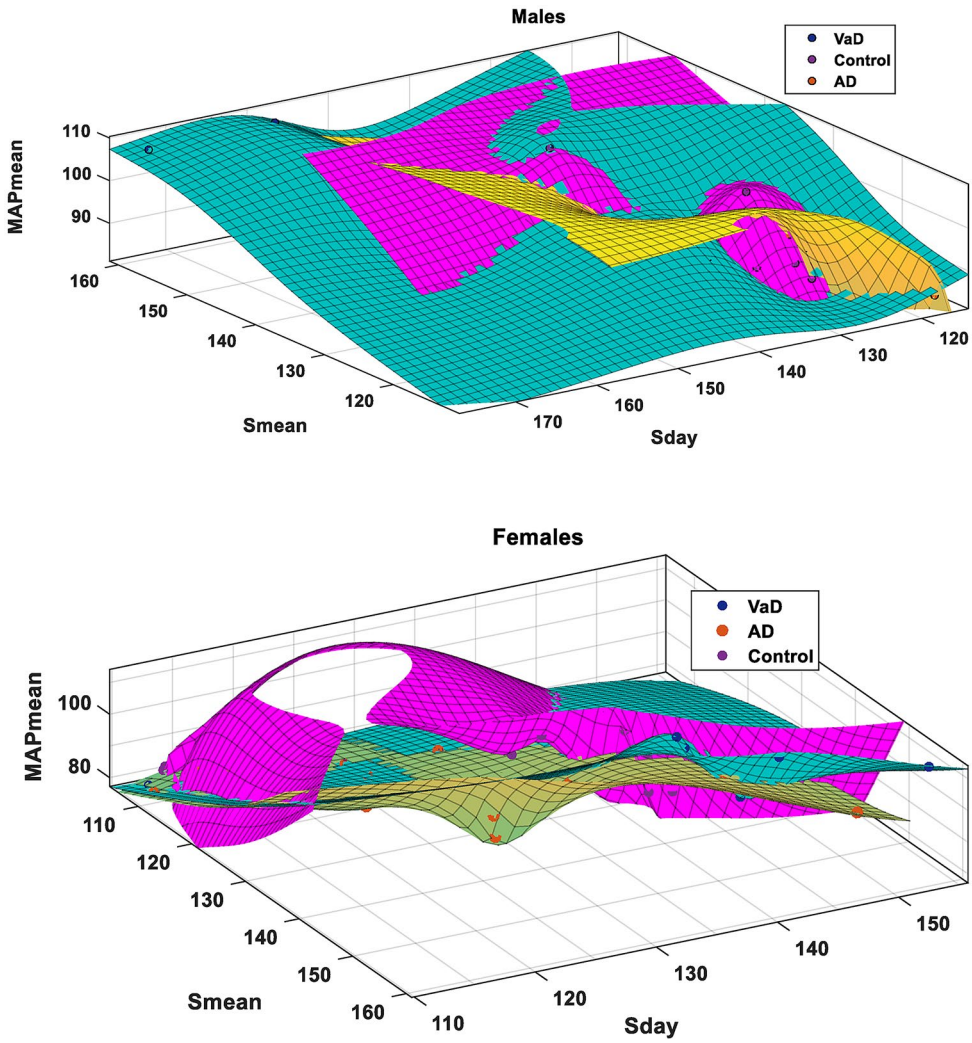

Fig. 2 Surface interpolation of 3D plot of measured points (Smean, Sday, MAPmean), for males and females. S = SBP: systolic blood pressure (mmHg), MAP: mean arterial pressure (mmHg)

Table 4 Overall accuracy of different classifications in the 3 classes: AD, VaD and Control, using the measured data, and also some selected principal components from the PCA preprocessing, in both approaches the selection being based on boxplot analysis against classes

	Classification based on LOWESS 3D regression, PCA	Classification based on LOWESS 3D regression, including MAPmean, Sday, Dday or PPday	Subspace discriminant based classifier, including MAPmean, Sday, Dday or PPday	SVM-based classifier, including MAPmean, Sday, Dday or PPday	KNN-based classifier, including MAPmean, Sday, Dday or PPday	Subspace-based classifier, PCA	SVM-based classifier, PCA	KNN-based classifier, PCA
All	0.37	0.43	0.47	0.55	0.51	0.52	0.53	0.56
Females	0.56	0.53	0.61	0.65	0.68	0.6	0.63	0.66
Males	0.47	0.48	0.61	0.59	0.59	0.57	0.64	0.55

Discussion

Aging is associated with major changes in arterial walls such as endothelial dysfunction, inflammation, compliance reduction, and increased arterial stiffness [24]. Aging promotes increases in SBP and decreases in DBP, leading to increased pulse pressure which is a risk factor for cardiovascular events and might be involved in the development of cognitive impairment [25]. Hypertension is the main factor that causes small vessel disease, responsible for leukoaraiosis, lacunar infarcts, and microinfarcts [26].

On the other hand, increased pulse pressure may affect the diastolic coronary perfusion and thus contribute to ischemic heart disease and heart failure [27]. Low DBP in late life may contribute to cerebral hypoperfusion which can accelerate disease processes leading to AD and VaD [11, 28]. Randomized clinical trials have shown that maintaining BP within normal limits in midlife is clinically important to reduce widespread atherosclerosis and the risk of late-life dementia [29].

Most of the patients included in our study received ACE inhibitors, similar to more recent studies where ACE inhibitors, ARBs, and calcium channel blockers were prescribed more frequently, in addition to diuretics [4].

Our results showed that VaD patients displayed higher SBP, MAP, and pulse pressure compared to controls and AD patients. Also, decreased values of DBP where found in AD patients especially during the night period. HR was increased in the groups of patients compared to healthy controls, especially during nighttime. Both groups of patients with dementia were associated with an alteration in the circadian pattern with the highest incidence of the non-dipper and reverse dipper pattern when compared with the healthy elderly. Sleep disturbances occur with Alzheimer's disease and vascular dementia, and the disruption in the sleep–wake cycle can determine more behavioral changes interfering with the BP pattern.

Hypertension is as common in people with dementia as in other populations, but early initiation of antihypertensive treatment can help prevent further cognitive decline [30–32]. Vascular changes in cortical blood flow are a preclinical feature of AD disease; focal decreases in cerebral blood flow can have an impact on amyloid clearance [33, 34]. Low values of DBP reflect higher degrees of arterial stiffness associated with cerebrovascular atherosclerosis. Also, DBP reduction during nighttime in patients with AD requires greater attention paid to monitoring BP using ABPM devices and also caution in administering antihypertensive therapy. In addition to the impaired cerebral autoregulation, excessive antihypertensive therapy may exacerbate the risk of cerebral hypoperfusion in patients with dementia [35]. A systematic review of observational studies regarding the treatment of hypertension in people with dementia [4] underlines that patients with dementia are not managed differently from those without dementia, despite their increased risk of adverse events related to treatment. Moreover, hypertensive patients with dementia have higher risk of falls, fractures, and overall mortality [30]. Further recommendations and guidelines are needed to establish the risk benefit of antihypertensive treatment in patients with dementia.

The main limitation of our study was the relatively small sample size, which makes it difficult to draw more specific conclusions. Another drawback is the limited number of patients with advanced dementia because of the difficult cooperation for testing. ABPM monitoring device is ideal to wear at home and not under hospital conditions as in our case. Also, patients with dementia enrolled in the study were treated with various drugs and the effect of those treatments on BP could not be neglected.

The small volumes of grouped subjects by disease category and sex, between minimum 12 and maximum of 18 subjects per group, provide large confidence intervals of means and overlapping boxplots, which prove insufficient results to draw reliable conclusions regarding the variables discrimination power, although a real but moderate discriminatory effect may probably exist. Further studies may rely on analyzing such groups from the perspective of the variables that produced the best accuracy result in what concerns classification. Combinations of 3 variables, such as MAP mean, SBD day and DBP day/night, or pulse pressure day/night, for both genders, seem to be the most promising candidates for discriminating AD from VaD and Control. The best classification results were provided by the SVM and KNN based classifiers, on these reduced sets of data. The classification was considered as validation for significant differences in the considered group of variables for the three categories taken into account: VaD, AD, and Control, eventually combined with sex discrimination.

Conclusions

Increased SBP, pulse pressure, and alteration in the circadian pattern with the highest incidence of the non-dipper and reverse dipper pattern were found in patients with dementia when compared with the healthy elderly. Also, decreased values of DBP where found in AD patients, especially during nighttime. Further studies describing the influence of BP pattern, specifically during nighttime on cognitive decline are needed. Personalized antihypertensive management according to ABPM parameters is essential in dementia patients, considering the disruption in the sleep–wake cycle often encountered in these patients.

Acknowledgements This work was supported by the University of Medicine and Pharmacy "Grigore T. Popa" Iasi Grants No. 29241.

Declarations

Conflict of interest The authors declare that have no conflict of interests.

References

1. Faraco G, Iadecola C (2013) Hypertension: a harbinger of stroke and dementia. Hypertension 62:810–817

2. Abholz HH, Wiese B, Fuchs A et al (2010) Are patients with dementia treated as well as patients without dementia for hypertension, diabetes, and hyperlipidaemia? Br J Gen Pract 60(578):671–674
3. Zhu CW, Livote EE, Kahle-Wrobleski K et al (2011) Utilization of antihypertensives, antidepressants, antipsychotics, and hormones in Alzheimer disease. Alzheimer Dis Assoc Disord 25(2):144–148
4. Welsh TJ, Gladman JR, Gordon AL (2014) The treatment of hypertension in people with dementia: a systematic review of observational studies. BMC Geriatr 14:19
5. Gottesman RF, Schneider AL, Albert M et al (2014) Midlife hypertension and 20 year cognitive change: the atherosclerosis risk in communities, neurocognitive study. JAMA Neurol 71(10):1218–1227
6. Kelley BJ, Petersen RC (2007) Alzheimer's disease and mild cognitive impairment. Neurol Clin 25:577–609
7. Chamorro A, Pujol J, Saiz A et al (1997) Periventricular white matter lucencies in patients with lacunar stroke. A marker of too high or too low blood pressure? Arch Neurol. 54(10):1284–1288
8. Matsubayashi K, Okumiya K, Wada T et al (1997) Postural dysregulation in systolic blood pressure is associated with worsened scoring on neurobehavioral function tests and leukoaraiosis in the older elderly living in a community. Stroke 28(11):2169–2173
9. Kohara K, Jiang Y, Igase M et al (1999) Postprandial hypotension is associated with asymptomatic cerebrovascular damage in essential hypertensive patients. Hypertension 33(1 Pt 2):565–568
10. denAbeelen AS, Lagro J, van Beek A, Claassen J (2014) Impaired cerebral autoregulation and vasomotor reactivity in sporadic Alzheimer's in disease. Curr Alzheimer Res 11(1):11–17
11. Qiu C, Winblad B, Fratiglioni L (2009) Low diastolic pressure and risk of dementia in very old people: a longitudinal study. Dement Geriatr Cogn Disord 28:213–219
12. Epstein NU, Lane KA, Farlow MR et al (2013) Alzheimer's Disease Neuroimaging Initiative. Cognitive dysfunction and greater visit-to-visit systolic blood pressure variability. J Am Geriatr Soc. 61(12):2168–2173
13. Hughes TM, Kuller LH, Barinas-Mitchell EJ et al (2014) Arterial stiffness and beta-amyloid progression in nondemented elderly adults. JAMA Neurol 71(5):562–568
14. McKhann G, Drachman D, Folstein M et al (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944
15. Roman GC, Tatemichi TK, Erkinjuntti T (1993) Vascular dementia—diagnostic criteria for research studies: report of the NINDS AIREN International Workshop. Neurology 43(2):250–260
16. Hachinski VC, Iliff LD, Zilkha E et al (1975) Cerebral blood flow in dementia. Arch Neurol 32:632–637
17. Schatz IJ, Bannister R, Freeman RL et al (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. Neurology 46(5):1470
18. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental-state"—a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
19. Slachevsky A, Dubois B (2004) Frontal assessment battery and differential diagnosis of frontotemporal dementia and Alzheimer disease. Arch Neurol 61(7):1104–1107
20. Yesavage JA (1988) Geriatric depression scale. Psychopharmacol Bull 24:709–711
21. Lawton MP, Moss M, Fulcomer M et al (1982) A research and service oriented multilevel assessment instrument. J Gerontol 37:91–99
22. Mancia G, De Backer G, Dominiczak A et al (2007) Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 28:1462–1536
23. Pogue V, Rahman M, Lipkowitz M et al (2009) African American Study of Kidney Disease and Hypertension Collaborative Research Group: disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension 53:20–27
24. Lakatta EG (2013) The reality of aging viewed from the arterial wall. Artery Res 7(2):73–80
25. Harvey A, Montezano AC, Touyz RM (2015) Vascular biology of ageing-Implications in hypertension. J Mol Cell Cardiol 83:112–121
26. Sörös P, Whitehead S, Spence JD et al (2013) Antihypertensive treatment can prevent stroke and cognitive decline. Nat Rev Neurol 9:174–178
27. Benetos A, Rudnichi A, Safar M et al (1998) Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 32:560–564
28. Verghese J, Lipton RB, Hall CB et al (2003) Low blood pressure and the risk of dementia in very old individuals. Neurology 61:1667–1672
29. Neal B, MacMahon S, Chapman N (2000) Blood Pressure Lowering Treatment Trialists'Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood pressure-lowering drugs: results of prospectively designed overviews of randomized trials. Lancet 356:1955–1964
30. Welsh TJ, Gordon AL, Gladman JRF (2019) Treatment of hypertension in people with dementia: a multicenter prospective observational cohort study. J Am Med Dir Assoc 20(9):1111–1115
31. Emdin CA, Rothwell PM, Salimi-Khorshidi G et al (2016) Blood pressure and risk of vascular dementia: evidence froma primary care registry and a cohort study of transient ischemic attack and stroke. Stroke 47(6):1429–1435
32. Li J, Wang YJ, Zhang M et al (2011) Chongqing ageing study group vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. Neurology 76(17):1485–1491
33. Hays CC, Zlatar ZZ, Wierenga CE (2016) The utility of cerebral blood flow as a biomarker of preclinical Alzheimer's disease. Cell Mol Neurobiol 36:167–179
34. Binnewijzend MAA, Benedictus MR, Kuijer JPA et al (2016) Cerebral perfusion in the predementia stages of Alzheimer's disease. Eur Radiol 26:506–514
35. Qiu C, Winblad B, Fratiglioni L (2009) Low diastolic pressure and risk of dementia in very old people: a longitudinal study. Dement Geriatr Cogn Disord 28(3):213–219