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ORIGINAL COMMUNICATION

Blood pressure circadian rhythm alterations in alpha-synucleinopathies

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Abstract

Introduction We sought to analyze the blood pressure (BP) circadian rhythm in Parkinson's disease (PD), multiple system atrophy (MSA), and pure autonomic failure (PAF) and to evaluate the effect of vasoactive and dopaminergic medications on BP fluctuations during activities of daily living.

Methods We analyzed data from patients with PD ($n=72$), MSA ($n=18$), and PAF ($n=17$) evaluated with 24-h ambulatory BP monitoring (ABPM) at our Center between 1996 and 2015. Comparisons between groups were performed according to (a) clinical diagnosis and (b) pharmacological treatment. ABPM parameters included 24-h BP variability, BP load, nocturnal dipping, and awakening hypotension.

Results The average BP was $121 \pm 14/72 \pm 8$ mmHg during daytime and $133 \pm 20/76 \pm 13$ mmHg during nighttime ($p<0.01$), with BP load of $24 \pm 22/15 \pm 16\%$ (daytime) vs. $61 \pm 36/52 \pm 36\%$ (nighttime) ($p<0.01$). In-office BP measurements were consistent with OH in 95 patients (89%) and SH in 63 (59%). ABPM demonstrated increased BP variability in 67 patients (63%), awakening hypotension in 63 (59%), "reverse dipping" in 85 (79.4%), "reduced dipping" in 13 (12.1%), and "normal dipping" in 9 (8.4%). No differences were observed between PD, MSA, and PAF, but a sub-analysis of PD patients revealed two distinct patterns of BP alterations. No significant differences were observed in relation to the use of vasoactive or dopaminergic medications.

Conclusion Regardless of the neurological diagnosis and pharmacological treatment, patients with alpha-synucleinopathies showed a BP circadian rhythm characterized by increased BP variability, reverse dipping, increased BP load, and awakening hypotension.

Keywords Cardiovascular autonomic neuropathy · Ambulatory blood pressure monitoring · Reverse dipping · Blood pressure variability · Orthostatic hypotension.

Introduction

Cardiovascular autonomic neuropathy (CAN) is a frequent yet underrecognized feature of Parkinson's disease (PD), multiple system atrophy (MSA), and pure autonomic failure (PAF), an heterogeneous group of neurodegenerative disorders commonly gathered under the eponymous of alpha-synucleinopathies [1]. Both central and peripheral mechanisms may participate in the autonomic dysregulation associated with these conditions, and eventually lead to a circadian blood pressure (BP) rhythm dysregulation characterized by increased blood pressure variability (BPV) across the supine, sitting, and standing positions, which may result in orthostatic hypotension (OH) and supine hypertension (SH) [2].

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Previous studies demonstrated that 24-h ambulatory blood pressure monitoring (ABPM) may capture a large variety of abnormal circadian BP patterns associated with CAN, including awakening hypotension, 24-h BPV, and nocturnal dipping [3, 4]. These findings support the notion that ABPM might significantly advance the diagnosis and follow-up of CAN. Still, the extent to which ambulatory BP alterations are differentially represented in PD, PAF, and MSA remain unclear, as well as the impact of vasoactive and dopaminergic medications on the 24-h circadian BP profile.

Using historical data from patients with PD, MSA, and PAF evaluated with 24-h ambulatory BP monitoring (ABPM) at our Center between 1996 and 2015, we sought to investigate the pattern of circadian BP alterations associated with different alpha-synucleinopathies, and the impact of dopaminergic and vasoactive medications on ambulatory BP fluctuations.

Materials and methods

Study population

We reviewed historical data from patients referred to the Autonomic Unit of the University of Torino (Italy) between January 1996 and January 2015 as per the following inclusion and exclusion criteria:

Inclusion criteria: diagnosis of PD, MSA, or PAF [5–7]; diagnosis of CAN according to a standardized battery of autonomic testing [8]; availability of ABPM data collected within two weeks from the autonomic assessment; and stable dose of vasoactive and dopaminergic drugs for at least 2 weeks before the autonomic assessment.

Exclusion criteria: incomplete data (lack of ABPM recordings or autonomic testing or clinical documentation); family history of autonomic neuropathy; and disorders associated with secondary autonomic neuropathy, such as chronic renal failure, diabetes, sarcoidosis, amyloidosis, HIV, autoimmune disorders, malignancies, Lyme disease [1].

Cardiovascular autonomic testing

The diagnosis of CAN was based on the following standardized battery of cardiovascular autonomic testing [8] (DAN Test Microlab, Padua, Italy):

- Heart rate variability during deep breathing: the expiratory to inspiratory ratio (E/I) was calculated from the maximum and minimum R–R interval during deep breathing at 6 breaths/min.
- Heart rate response during orthostatism: the 30:15 ratio was calculated as the ratio between the longest R–R interval (around the 30th beat after standing) and the shortest R–R interval (around the 15th beat after standing).
- Heart rate variability during the Valsalva Maneuvre: The Valsalva ratio was calculated as the ratio between the longest R–R interval (shortly after the maneuver, which consists of blowing into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg, holding the pressure for 15 s) and the shortest R–R interval (during the strain period).
- BP response during orthostatism: BP was measured by a semiautomatic sphygmomanometer in the supine position and after 1 and 3 min of standing.

Tests were classified as normal (score = 0), borderline (score = 1), and abnormal (score = 2), using age-related normal ranges [9]. The diagnosis of CAN was made when at least two tests were abnormal, or the total score was greater than 2 [8]. OH was defined as a reduction of systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg within 3 min of standing [10]. SH was defined as a systolic BP ≥ 140 and/or a diastolic BP ≥ 90 mmHg in the supine position in patients with concomitant neurogenic OH (OH associated with CAN) [11]. The item 1 of the Orthostatic Hypotension Symptom Assessment (OHSA) ("severity of dizziness, lightheadedness, feeling faint, or feeling like you might blackout") was used to discriminate between symptomatic OH (OHSA score ≥ 1) from asymptomatic OH (OHSA score = 0) [12].

Ambulatory blood pressure monitoring (ABPM)

All patients underwent ABPM using non-invasive portable recorder Spacelabs 90207 (Spacelabs Inc., Redmond, WA, USA©) with an appropriately sized cuff placed on the non-dominant arm, according to the current guidelines [13]. BP measurements were taken every 15 min; all patients were instructed to record the following data in a diary: sleep and wake time, time of meals, medications, main behavioral and occupational activities, quality of sleep, and symptoms. Normal reference thresholds for ABPM parameters (mean daytime and nighttime BP), as well as the definitions of BPV and dipping patterns were referred to data available from the population of patients with essential arterial hypertension [14] due to the lack of validated normative ABPM data in patients with CAN. Daytime and nighttime periods were defined on the basis of the patient's diary.

Blood pressure load was measured as the percentage of BP values higher than normal limits during daytime and nighttime (normal value < 30%) [14].

Blood pressure variability was defined as standard deviation of nocturnal systolic BP (normal ≤ 11); weighted-blood pressure variability (w-BPV) was defined as the sum of standard deviation of diurnal and nocturnal systolic BP,

corrected for daytime and nighttime durations (normal ≤ 11) [13].

Dipping pattern, corresponding to the average reduction in systolic BP between waking and sleeping hours, was classified as per the recommendations of the European Society of Hypertension [13]:

- Extreme dipping: systolic nighttime BP/systolic daytime BP ≤ 0.8, corresponding to an average systolic BP reduction during sleep greater or equal to 20%.
- Normal dipping: systolic nighttime BP/systolic daytime BP > 0.8 but ≤ 0.9, corresponding to an average systolic BP reduction during sleep of 10–19%.
- Reduced dipping: systolic nighttime BP/systolic daytime BP > 0.9 but ≤ 1.0, corresponding to an average systolic BP reduction during sleep of 0–9%.
- Reverse dipping: systolic nighttime BP/systolic daytime BP ≥ 1.0, corresponding to an average increase in nighttime systolic BP values.

Awakening hypotension was defined as a systolic BP drop ≥ 20 mmHg within 60′ after standing up in the morning, compared to the mean of the last three BP measurements before standing.

Statistical analysis

We characterized the circadian BP profile reporting the daytime and nighttime systolic and diastolic BP, and the daytime and nighttime BP load, as well as the prevalence of patients with increased BPV (absolute and weighted values), awakening hypotension, reverse dipping pattern, OH, and SH. Continuous data were expressed as mean ± standard deviations, prevalence as percentages.

The circadian BP profile was then compared among the three subtypes of primary autonomic neuropathy (PD, MSA, and PAF) using one-way ANOVA or Fisher's exact test, as appropriate. Bonferroni's correction was applied to adjust for multiple comparisons.

An unsupervised cluster analysis with a K-means approach was performed to study BP circadian profile in PD. A K-means clustering algorithm was used to find hidden structure in data and divide patients into two groups (PD cluster 1 and PD cluster 2). The main steps in the K-mean analysis were as follows: (1) ABPM and office BP parameters were selected to build the model; (2) two cluster centers were randomly defined; (3) each patient was assigned to the nearest cluster center; (4) we computed new cluster centers and re-iterated step 3 until centers convergence; (5) patients were grouped into clusters [15], as per the models previously described [16, 17]. An analysis of covariance (ANCOVA) was used to confirm differences in ABPM and office BP values between the two PD clusters after adjusting for age and dopamine-agonists Levodopa Equivalent Daily Dose (LEDD) [18], and among the three diseases after adjusting for age and disease duration.

Also, we studied the impact of vasoactive and dopaminergic medications on ABPM parameters. For this aim, patients were divided into: (a) no dopaminergic medications, levodopa, dopamine agonists, and levodopa plus dopamine-agonists group; and (b) no vasoactive drugs, anti-hypertensives, anti-hypotensives, and anti-hypertensives plus anti-hypotensives group. We compared the mean daytime and nighttime systolic and diastolic BP, the mean daytime and nighttime BP load, and the supine and orthostatic (1′ and 3′) BP values by means of the one-way ANOVA; the prevalence of patients with increased BPV (both absolute and weighted values), awakening hypotension, reverse dipping pattern, OH, and SH were compared using the Fisher's exact test. Bonferroni's correction was applied to adjust for multiple comparisons. Moreover, we analyzed differences of levodopa, dopamine agonists, and total LEDD in patients with or without OH, SH, increased w-BPV, awakening hypotension, reverse dipping pattern, by means of the Mann–Whitney test. Continuous variables were expressed as mean ± standard deviation, while qualitative variables were expressed as absolute values of frequency and percentage values. p values lower than 0.05 were considered as statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS—version 22—© 2014 IBM). Cluster analysis was performed using MATLAB R2017b and PYTHON 2.7.

Results

Among 302 subjects screened, a total of 107 patients (67% males and 33% women) with PD ($n = 72$), MSA ($n = 18$), or PAF ($n = 17$) were included in the analysis (Fig. 1; Table 1); 95 patients (89%) met the criteria for OH, and 63 (59%) for SH. All subjects were diagnosed with CAN according to the results of autonomic testing (Fig. 2).

Ambulatory blood pressure circadian rhythm

The average BP was 121 ± 14/72 ± 8 mmHg (daytime) and 133 ± 20/76 ± 13 mmHg (nighttime) ($p < 0.01$), with a BP load of 24 ± 22/15 ± 16% (daytime) and 61 ± 36/52 ± 36% (nighttime) ($p < 0.01$). ABPM recordings showed increased BPV in 67 patients (63%), increased w-BPV in 94 (88%), and awakening hypotension in 63 (59%). The dipping pattern was "reversed" in 85 patients (79.4%), "reduced" in 13 (12.1%), and "normal" in 9 (8.4%).

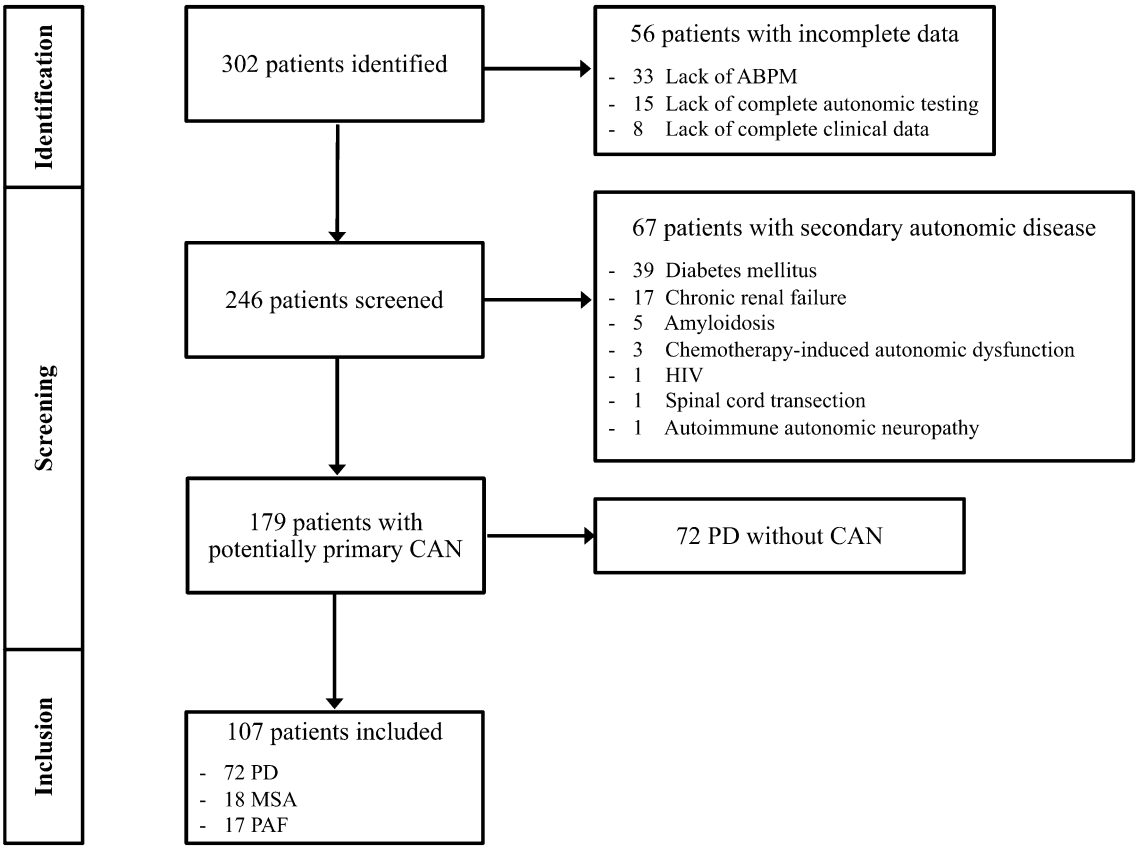

Fig. 1 Flow chart of patients selection process

Circadian blood pressure rhythm in PD, MSA, and PAF

PD patients were older and with longer disease duration than MSA ones. The prevalence of symptomatic OH was lower in PD compared to the other conditions. No significant differences were detected in the ABPM profile of patients with PD, MSA, and PAF [Table 1], even after adjusting for age and disease duration. Two distinct patterns were detected in PD: the first (PD1) characterized by BP loads within the normal range, low prevalence of SH, and milder ABPM alterations; the second (PD2) associated with increased nighttime BP, BP loads, SH, reverse dipping, awakening hypotension, and w-BPV. PD1 was characterized by lower BP values both in supine and orthostatic (3′) positions, but the symptomatic OH was equally distributed between the two groups. Patients PD2 were older ($p < 0.05$) and treated with lower dosages of dopamine agonists ($p < 0.05$). However, no differences were observed in the severity of cardiovascular autonomic testing [Table 2]. Differences remained significant even after adjusting for age and dopamine agonists LEDD [Supplementary Table 1].

Effect of vasoactive and dopaminergic medications

There were increased supine in-office BP values in patients treated with anti-hypotensive agents (systolic: 159 ± 27 vs. 140 ± 22 mmHg, $p = 0.04$; diastolic: 93 ± 13 vs. 83 ± 10 mmHg, $p = 0.01$). No other differences were found in ABPM or in-office variables (Table 3; Supplementary Tables 2, 3, 4, 5, 6). OH and awakening hypotension were associated with lower LEDD (Tables 4, 5).

Discussion

Our data confirm the association between CAN and increased BPV, nocturnal BP, BP load, awakening hypotension, and reverse dipping, independently from the underlying neurological diagnosis and pharmacological treatment. While in-office BP measurements and ABPM profiles were overall similar in the three alpha-synucleinopathies, two distinctive patterns of circadian BP alterations emerged in PD; the first one characterized by milder ABPM dysfunctions and normal in-office BP measurements, the second by widespread ABPM and in-office BP dysfunctions.

Table 1 Demographic and clinical characteristics

	PD ($n=72$)	MSA ($n=18$)	PAF ($n=17$)	p value
Age (years)	70 ± 8*	63 ± 10*	67 ± 13	0.01
Female sex (n) (%)	18 (25)§	7 (39)	10 (59)§	0.02
Disease duration (years)	7.8 ± 6*	3.3 ± 4*	4.7 ± 4	< 0.01
Dopaminergic therapy (n) (%)	66 (92)	8 (44)	NA	< 0.01
Total LEDD (mg)	712 ± 459*	335 ± 525*	NA	< 0.01
Levodopa LEDD (mg)	599 ± 412*	323 ± 512*	NA	0.03
Dopamine agonists LEDD (mg)	91 ± 131*	5 ± 19*	NA	< 0.01
Vasoactive therapy (n) (%)	23 (32)	11 (61)	7 (41)	0.07
Previous arterial hypertension (n) (%)	15 (21)	5 (28)	4 (24)	0.81
SH (n) (%)	41 (57)	11 (61)	11 (65)	0.76
OH (n) (%)	61 (85)	18 (100)	17 (100)	0.07
Symptomatic OH (n) (%)	52 (72)§	17 (94)	17 (100)§	0.01
Total autonomic score	4.6 ± 1.7	5.2 ± 2.1	5.5 ± 1.4	0.11
Ambulatory blood pressure monitoring				
Nocturnal recording time (h)	7.8 ± 1.6	7.9 ± 1.7	8.1 ± 0.9	0.80
Diurnal recording time (h)	16.1 ± 1.6	15.7 ± 1.6	15.9 ± 0.9	0.54
Valid recordings (%)	89.8 ± 10.1	93.1 ± 5.4	87.9 ± 8.2	0.27
Daytime SBP (mmHg)	120 ± 13	117 ± 10	128 ± 21	0.07
Daytime MBP (mmHg)	88 ± 8	88 ± 8	92 ± 13	0.30
Daytime DBP (mmHg)	72 ± 8	73 ± 8	73 ± 11	0.68
Nighttime SBP (mmHg)	131 ± 18	134 ± 21	142 ± 23	0.10
Nighttime MBP (mmHg)	94 ± 13	100 ± 18	100 ± 15	0.18
Nighttime DBP (mmHg)	75 ± 12	82 ± 17	76 ± 12	0.13
Daytime SBP load (%)	23 ± 21	23 ± 20	31 ± 28	0.39
Daytime DBP load (%)	15 ± 15	18 ± 17	13 ± 18	0.64
Nighttime SBP load (%)	59 ± 35	67 ± 34	63 ± 42	0.70
Nighttime DBP load (%)	53 ± 36	60 ± 36	39 ± 35	0.18
Reverse dipping (n) (%)	54 (75)	16 (89)	15 (88)	0.27
High w-BPV (n) (%)	61 (85)	16 (89)	17 (100)	0.22
Awakening hypotension (n) (%)	42 (60)	11 (79)	10 (77)	0.26
Office blood pressure values				
SBP (supine) (mmHg)	142 ± 22	145 ± 21	158 ± 31	0.06
DBP (supine) (mmHg)	83 ± 11	90 ± 13	88 ± 14	0.06
SBP (orthostatism 1′) (mmHg)	104 ± 25	106 ± 16	100 ± 26	0.75
DBP (orthostatism 1′) (mmHg)	68 ± 13	70 ± 11	63 ± 14	0.24
SBP (orthostatism 3′) (mmHg)	103 ± 24	94 ± 26	89 ± 30	0.11
DBP (orthostatism 3′) (mmHg)	67 ± 13	64 ± 14	60 ± 14	0.19

p value: statistical difference among the three groups

PD Parkinson's disease with autonomic neuropathy, *MSA* multiple system atrophy, *PAF* pure autonomic failure, *LEDD* levodopa equivalent daily dose, *SH* supine hypertension, *OH* orthostatic hypotension, *SBP* systolic blood pressure, *MBP* mean blood pressure, *DBP* diastolic blood pressure, *w-BPV* weighted blood pressure variability, *NA* not applicable

*Significant difference ($p < 0.05$) between PD and MSA (after Bonferroni's correction)

§Significant difference ($p < 0.05$) between PD and PAF (after Bonferroni's correction)

Circadian blood pressure alterations

The prevalence of reverse dipping was 79%, not influenced by the underlying pharmacological treatment or neurological diagnosis. These data confirm the results of previous studies showing increased nocturnal BP in patients with alpha-synucleinopathies [19–21]. Plaschke and colleagues [22] suggested that increased nocturnal BP might differentiate patients with and without CAN, being the autonomic dysfunction itself, rather than the underlying neurodegenerative

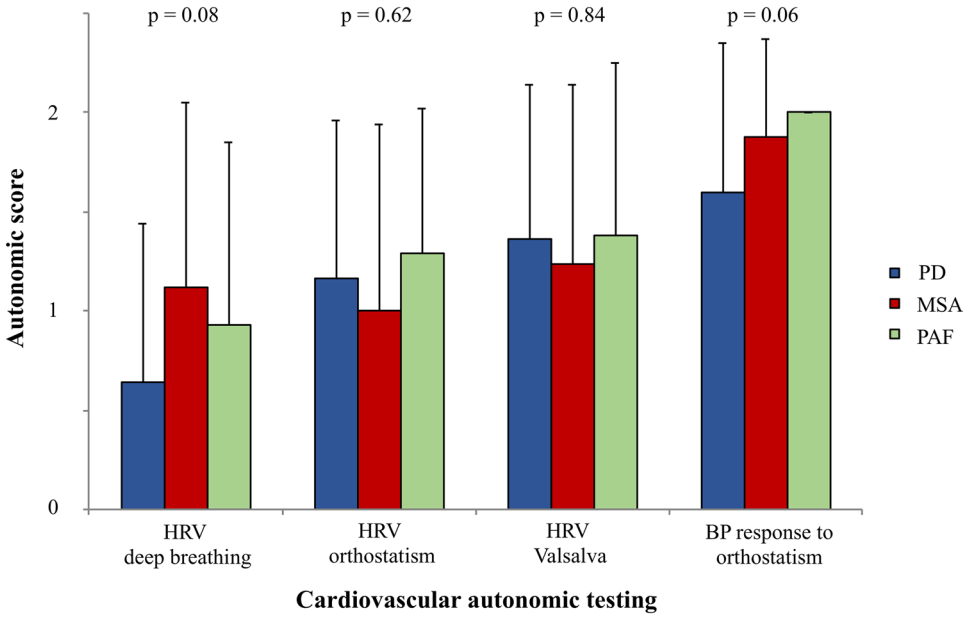

Fig. 2 Results of cardiovascular autonomic testing

disorder, responsible for abnormalities observed in the circadian BP rhythm [23]. Pathophysiological mechanisms may include reduced baroreflex sensitivity, increased peripheral vascular resistance, reduced nitrogen monoxide production, and alteration of the renin-angiotensin-aldosterone system [2, 24–26]. In a recent study of our group, we showed that reverse dipping can discriminate autonomic dysfunction with high accuracy, thus representing a useful tool for the early screening of CAN [4]. In addition, 59% of our population was affected by awakening hypotension, a frequent yet underrecognized complication of CAN due to the tail-effect of bedtime anti-hypertensive medications and to nighttime pressure natriuresis, which ultimately results in body fluid volume depletion [27]. These data are in agreement with the findings of Tulen and colleagues, who reported four cases of PAF with severe difficulty in getting up in the morning due to postural hypotension [28]. Also, our findings prove relevant when considering that increased nocturnal BP load and increased BP variability may result in cardiovascular alterations similar to those associated with essential hypertension [29–31]. Previous studies found that SH can result in impaired renal function in PAF [32] and cerebrovascular damage in PD and MSA [33], and that reverse dipping correlates with cardiac [34], renal [32] and cerebrovascular damage [35, 36].

Comparison between PD, MSA, and PAF

While gathered under the common eponymous of alpha-synucleinopathies, PD, MSA, and PAF are three considerably different clinical entities. PD presents with bradykinesia, rigidity, and resting tremor, variably associated with autonomic features, MSA with prominent autonomic failure in combination with parkinsonism, pyramidal symptoms, or cerebellar symptoms, and PAF with severe autonomic failure not associated with central neurological features [37].

From a pathological standpoint, MSA is characterized by central nervous system alterations, such as catecholaminergic deficiency, and degeneration of the brainstem and sacral parasympathetic nuclei, PAF involves the autonomic nervous system peripheral components such as sympathetic ganglia and distal axons, and PD presents with a variable combination of both central and peripheral alterations [38–40]. The clinical–pathological boundaries of PAF, on the other hand, remain unclear. A recent prospective study showed that 34% of patients initially diagnosed with PAF converted to PD (8%), MSA (8%), or dementia with Lewy bodies (18%) [41] challenging, therefore, the initial notion that PAF is a Lewy body disorder restricted to the peripheral components of the autonomic nervous system [42].

Vasoactive and dopaminergic drugs

While patients treated with antihypotensive medications showed increased in-office BP, the 24-h ABPM was not associated with relevant differences in the diurnal and nocturnal BP or in BP load. These data confirm the results of a recent case series showing the lack of correspondence between in-office supine BP and ABPM values [43]. Possible explanations may include the effect of daytime hypotensive stressors, such as meals, pharmacological therapies, and environmental temperature, as well as the effect of bedtime anti-hypertensive treatments prescribed to treat nocturnal SH. We adhered to the current recommendations, which suggest using short half-life and bedtime anti-hypertensive drugs for the treatment of SH [44]. Still, the possibility that

Table 2 Blood pressure clusters in Parkinson's disease

	PD total ($n=72$)	PD cluster 1 ($n=37$)	PD cluster 2 ($n=35$)	p value
Age (years)	70 ± 8	67 ± 8	73 ± 6	< 0.01
Female sex (n) (%)	18 (25)	12 (32)	6 (17)	0.13
Disease duration (years)	7.8 ± 6	8.2 ± 6	7.4 ± 5	0.50
Dopaminergic therapy (n) (%)	66 (92)	34 (92)	32 (91)	0.94
LEDD (mg)	712 ± 459	714 ± 478	713 ± 449	0.98
Levodopa LEDD (mg)	599 ± 412	541 ± 427	660 ± 394	0.25
Dopamine-agonist LEDD (mg)	91 ± 131	133 ± 146	45 ± 95	0.01
Vasoactive therapy (n) (%)	23 (32)	10 (27)	13 (37)	0.36
Previous arterial hypertension (n) (%)	15 (21)	6 (16)	9 (26)	0.32
SH (n) (%)	41 (57)	15 (41)	26 (74)	< 0.01
OH (n) (%)	61 (85)	30 (81)	31 (89)	0.22
Symptomatic OH (n) (%)	52 (72)	28 (76)	24 (69)	0.14
Autonomic score	4.6 ± 1.7	4.5 ± 1.6	4.7 ± 1.9	0.57
Ambulatory blood pressure monitoring				
Daytime SBP (mmHg)	120 ± 13	115 ± 10	126 ± 13	< 0.01
Daytime MBP (mmHg)	88 ± 8	84 ± 7	92 ± 8	< 0.01
Daytime DBP (mmHg)	72 ± 8	69 ± 7	75 ± 7	< 0.01
Nighttime SBP (mmHg)	131 ± 18	118 ± 12	144 ± 14	< 0.01
Nighttime MBP (mmHg)	94 ± 13	85 ± 10	104 ± 9	< 0.01
Nighttime DBP (mmHg)	75 ± 12	68 ± 10	82 ± 8	< 0.01
Daytime SBP load (%)	23 ± 21	10 ± 11	36 ± 21	< 0.01
Daytime DBP load (%)	15 ± 15	8 ± 11	23 ± 14	< 0.01
Nighttime SBP load (%)	59 ± 35	31 ± 24	88 ± 13	< 0.01
Nighttime DBP load (%)	53 ± 36	26 ± 25	82 ± 18	< 0.01
Reverse dipping (n) (%)	54 (75)	22 (60)	32 (91)	< 0.01
High w-BPV (n) (%)	61 (85)	28 (76)	33 (94)	0.03
Awakening hypotension (n) (%)	42 (60)	16 (44)	26 (77)	0.01
Office blood pressure values				
SBP (supine) (mmHg)	142 ± 22	133 ± 21	152 ± 20	< 0.01
DBP (supine) (mmHg)	83 ± 11	78 ± 11	87 ± 10	< 0.01
SBP (orthostatism 1′) (mmHg)	104 ± 25	99 ± 22	110 ± 27	0.06
DBP (orthostatism 1′) (mmHg)	68 ± 13	66 ± 12	71 ± 14	0.09
SBP (orthostatism 3′) (mmHg)	103 ± 24	96 ± 23	110 ± 24	0.01
DBP (orthostatism 3′) (mmHg)	67 ± 13	63 ± 12	71 ± 13	0.01

p value: statistical difference between PD cluster 1 and 2

PD Parkinson's disease with autonomic neuropathy, *LEDD* levodopa equivalent daily dose, *SH* supine hypertension, *OH* orthostatic hypotension, *SBP* systolic blood pressure, *MBP* mean blood pressure, *DBP* diastolic blood pressure, *w-BPV* weighted blood pressure variability

anti-SH treatments taken bedtime increased the rate of awakening hypotension episodes, as previously described by Jordan and colleagues [45], cannot be excluded.

The effect of dopaminergic medications on circadian BP rhythm was only partially assessed due to biases associated with a real-life observational study. We found that OH patients were receiving lower doses of L-dopa and dopamine agonists. This data may reflect the attempt to minimize the severity of autonomic symptoms using low dosages of dopaminergic medications, which have the potential to reduce BP through central and peripheral mechanisms [46], such as reduction in the myocardial contractility and peripheral vasodilatation [47].

Cluster analysis in Parkinson's disease

We detected two distinctive patterns of circadian BP alterations in patients with PD; the first one characterized by milder ABPM dysfunctions and normal in-office BP measurements, the second one by widespread ABPM and in-office BP dysfunctions. Previous research endeavors focused on the importance of non-motor symptoms in different subtypes

Table 3 Pharmacological therapies: vasoactive drugs

	No vasoactive drugs ($n=66$)	Anti-hypertensives ($n=19$)	Anti-hypotensives ($n=16$)	Anti-hypertensives + anti-hypotensives ($n=6$)	p value
Ambulatory blood pressure monitoring					
Daytime SBP (mmHg)	120 ± 15	123 ± 13	123 ± 16	75 ± 8	0.76
Daytime MBP (mmHg)	88 ± 10	89 ± 9	92 ± 10	91 ± 7	0.43
Daytime DBP (mmHg)	71 ± 8	71 ± 8	76 ± 9	75 ± 8	0.17
Nighttime SBP (mmHg)	132 ± 20	128 ± 20	138 ± 19	147 ± 12	0.13
Nighttime MBP (mmHg)	95 ± 14	91 ± 14	102 ± 16	107 ± 5	0.12
Nighttime DBP (mmHg)	75 ± 12	71 ± 11	82 ± 15	86 ± 7	0.08
Daytime heart rate (b/min)	74 ± 9	76 ± 9	74 ± 10	73 ± 9	0.78
Nighttime heart rate (b/min)	66 ± 8	68 ± 9	68 ± 10	69 ± 8	0.73
Daytime SBP load (%)	24 ± 21	26 ± 22	23 ± 27	31 ± 18	0.85
Daytime DBP load (%)	15 ± 15	15 ± 16	15 ± 17	26 ± 20	0.44
Nighttime SBP load (%)	62 ± 35	56 ± 36	57 ± 38	77 ± 38	0.62
Nighttime DBP load (%)	51 ± 36	54 ± 32	46 ± 37	70 ± 40	0.56
Reverse dipping (%)	79	63	94	100	0.08
High w-BPV (%)	89	74	94	100	0.17
Awakening hypotension (%)	67	56	62	80	0.71
Office blood pressure values					
SBP (supine) (mmHg)	140 ± 22*	148 ± 27	159 ± 27 *	155 ± 22	0.04
DBP (supine) (mmHg)	83 ± 10*	82 ± 15	93 ± 13 *	90 ± 14	0.01
SBP (orthostatism 1′) (mmHg)	99 ± 23	116 ± 26	108 ± 25	105 ± 15	0.05
DBP (orthostatism 1′) (mmHg)	65 ± 13	75 ± 13	69 ± 14	68 ± 12	0.05
SBP (orthostatism 3′) (mmHg)	96 ± 25	114 ± 19	98 ± 30	97 ± 19	0.05
DBP (orthostatism 3′) (mmHg)	63 ± 14	71 ± 10	66 ± 14	64 ± 12	0.15
OH (%)	89	84	100	100	0.34
SH (%)	50 *	68	81 *	83	0.03

p value: statistical difference among the four groups

SBP systolic blood pressure, *MBP* mean blood pressure, *DBP* diastolic blood pressure, *w-BPV* weighted blood pressure variability, *OH* orthostatic hypotension, *SH* supine hypertension

*Significant difference ($p<0.05$) between no vasoactive drugs and anti-hypotensives group (after Bonferroni's correction)

of PD [48] but, to the best of our knowledge, this is the first study employing real-life ambulatory BP monitoring to detect differences between subgroups of PD patients with cardiovascular autonomic dysfunction. Critically, our findings remained significant even after adjusting for age and dopamine-agonists LEDD.

ABPM vs. in-office blood pressure measurements

There is increasing evidence that ABPM should be employed in the screening and monitoring of alpha-synucleinopathies-associated CAN [4]. ABPM advantages include the possibility of monitoring BP in a real-life unrestricted environment, assessing BPV associated with specific stimuli such as meals, vasoactive drugs, short-half-life antihypertensive medications, exposure to temperature variability, physical activity, and daily activities activity [49]. In fact, in-office BP measurements demonstrated to predict the severity of ambulatory orthostatic hypotension only in one-third of patients [50], emphasizing the poor correlation between patients' symptoms, blood pressure readings, OH-related complications, and OH-associated quality of life impairment [51, 52]. In this context, ABPM can both be seen as a diagnostic biomarker of PD-associated autonomic dysfunction, as suggested in a recent publication of our group [4], and as a tool to assist the management of vasopressor agents basing on real-life BP recording from an ecologically valid environment [44].

Limitations

Several limitations should temper the interpretation of our results. First, the analysis of historical data collected from a tertiary referral center for autonomic disorders. In fact, both the observational study design and the highly selected

Table 4 Pharmacological therapies: dopaminergic drugs

	No dopaminergic drugs ($n=16$)	Levodopa ($n=33$)	Dopamine-agonists ($n=4$)	Levodopa + Dopamine agonists ($n=37$)	p value
Ambulatory blood pressure monitoring					
Daytime SBP (mmHg)	120 ± 11	121 ± 14	120 ± 4	119 ± 12	0.89
Daytime MBP (mmHg)	91 ± 11	89 ± 9	91 ± 5	87 ± 8	0.43
Daytime DBP (mmHg)	74 ± 9	72 ± 7	76 ± 5	70 ± 7	0.32
Nighttime SBP (mmHg)	133 ± 22	137 ± 21	116 ± 13	128 ± 13	0.07
Nighttime MBP (mmHg)	99 ± 17	99 ± 15	88 ± 10	92 ± 11	0.09
Nighttime DBP (mmHg)	79 ± 18	78 ± 13	73 ± 9	73 ± 11	0.25
Daytime heart rate (b/min)	77 ± 10	73 ± 7	81 ± 17	75 ± 9	0.28
Nighttime heart rate (b/min)	69 ± 12	67 ± 7	68 ± 12	68 ± 8	0.93
Daytime SBP load (%)	25 ± 18	27 ± 24	11 ± 5	20 ± 20	0.28
Daytime DBP load (%)	22 ± 19	16 ± 15	17 ± 12	13 ± 14	0.27
Nighttime SBP load (%)	66 ± 33	65 ± 36	28 ± 34	58 ± 34	0.21
Nighttime DBP load (%)	60 ± 37	62 ± 38	54 ± 27	46 ± 34	0.30
Reverse dipping (%)	74	82	50	78	0.54
High w-BPV (%)	94	88	50	84	0.16
Awakening hypotension (%)	62	81*	75	47*	0.01
Office blood pressure values					
SBP (supine) (mmHg)	150 ± 27	146 ± 22	144 ± 28	137 ± 18	0.19
DBP (supine) (mmHg)	91 ± 13	83 ± 12	88 ± 17	82 ± 11	0.11
SBP (orthostatism 1′) (mmHg)	103 ± 16	108 ± 23	90 ± 23	104 ± 27	0.55
DBP (orthostatism 1′) (mmHg)	69 ± 10	68 ± 12	63 ± 10	69 ± 15	0.84
SBP (orthostatism 3′) (mmHg)	86 ± 19	104 ± 22	99 ± 21	104 ± 27	0.11
DBP (orthostatism 3′) (mmHg)	60 ± 11	67 ± 12	68 ± 12	68 ± 15	0.34
OH (%)	100	94	75	81	0.06
SH (%)	63	64	50	51	0.51

p value: statistical difference among the four groups

SBP systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *w-BPV* weighted blood pressure variability, *OH* orthostatic hypotension, *SH* supine hypertension

*Significant difference ($p<0.05$) between Levodopa and Levodopa + Dopamine agonists group (after Bonferroni's correction)

population of patients should limit the generalizability of our findings. Second, the lack of normative ABPM data for patients with CAN, which lead us to adhere to the normative values used in essential hypertension. Third, the lack of validated diagnostic definition for awakening hypotension. Fourth, the absence of a control group of PD patients without autonomic neuropathy, which might have provided additional insights regarding "early" signs of BP circadian rhythm dysfunction in patients not meeting the criteria for CAN. Fifth, the relatively "unstable" diagnosis of PAF, which may convert to a different synucleinopathy in over one-third of cases [41]. Sixth, the unequal representation of PD, MSA, and PAF, inevitably related to the different prevalence of these three clinical conditions. The incidence of PD has been estimated in 8–19/100.000 person-years [53], as compared to 3/100.000 person-years in MSA [54] and less than 1/100.000 in PAF. The largest prospective study of PAF [41], conducted from the top five autonomic centers in the United States, achieved an enrollment goal of "only" 74 patients over a 4-year recruitment period. Seventh, the lack of sample size calculations due to limited preliminary data and lack of validated clinical definitions and normative values for the majority of evaluated BP parameters. Eight, the relatively low sample size, which inevitably limited the possibility of running additional multivariate comparisons to investigate the differential effect of vasoactive and dopaminergic medications.

Conclusions

Our study indicates that specific circadian BP alterations might be observed in patients with CAN, predominantly consisting of reverse dipping, increased 24-h BPV, and awakening hypotension. No relevant differences were observed between PD, MSA, and PAF, although a cluster

Table 5 Dopaminergic therapies

		Total LEDD	Levodopa LEDD	Dopamine-agonists LEDD
Orthostatic hypotension	Yes	607 ± 471	530 ± 441	50 ± 90
	No	1010 ± 475	710 ± 433	251 ± 174
	p value	0.03	0.25	< 0.01
Supine hypertension	Yes	635 ± 504	546 ± 445	65 ± 111
	No	693 ± 469	564 ± 443	90 ± 139
	p value	0.73	0.86	0.56
Awakening hypotension	Yes	600 ± 473	519 ± 442	56 ± 119
	No	793 ± 479	643 ± 428	110 ± 127
	p value	0.06	0.23	0.02
High w-BPV	Yes	627 ± 496	533 ± 450	68 ± 116
	No	732 ± 482	575 ± 431	107 ± 151
	p value	0.44	0.77	0.40
Reverse dipping pattern	Yes	654 ± 500	558 ± 451	71 ± 125
	No	604 ± 476	482 ± 431	80 ± 117
	p value	0.67	0.56	0.68

LEDD Levodopa equivalent daily dose, *w-BPV* weighted blood pressure variability

analysis revealed two distinctive patterns of PD-associated BP dysregulation. Future prospective studies are required to confirm our results and clarify the prognostic implications of our findings, as well as the potential application of ABPM in the study of CAN.

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Compliance with ethical standards

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Ethical standard The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The local institutional review board (*Comitato Etico Interaziendale Città della Salute e della Scienza di Torino*) approved the study and all participants provided written informed consent.

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