Hypertension Research (2019) 42:1552–1560
https://doi.org/10.1038/s41440-019-0267-x

ARTICLE

Detection of orthostatic hypotension with ambulatory blood pressure monitoring in parkinson's disease

Fabrizio Vallelonga[1] · Alberto Romagnolo[2] · Aristide Merola[3] · Gabriele Sobrero[1] · Cristina Di Stefano[1] · Valeria Milazzo[1] · Jacopo Burrello[1] · Alessio Burrello[4] · Maurizio Zibetti[2] · Alberto Milan[1] · Franco Veglio[1] · Simona Maule[1]

Received: 15 December 2018 / Revised: 10 April 2019 / Accepted: 17 April 2019 / Published online: 22 May 2019

Abstract

We sought to test the accuracy of 24-hours ambulatory blood pressure (BP) monitoring (ABPM) for the detection of orthostatic hypotension (OH) in Parkinson's disease (PD). A total of 113 patients referred for autonomic testing between January 2015 and June 2017 underwent ABPM and office BP measurements in supine and standing positions. The study population consisted of 81 males and 32 females with PD duration of 6.5 ± 4.1 years and Hoehn and Yahr staging of 1 (13.3%), 1.5 (20.4%), 2 (27.4%), 2.5 (23.9%), 3 (13.3%), and 4 (1.8%). Motor fluctuations were present in 44% of patients. The data from office BP recordings were compared to selected ABPM parameters, and the results showed an association between OH and (a) ABPM-detected hypotensive episodes (Hypo-ep) and (b) ABPM-detected awakening hypotension (Hypo-aw). Having 2 or more Hypo-ep episodes ≤15 mmHg (systolic) compared to average 24-h systolic BP (Hypo-ep$^{\Delta 15/24\,h}$) yielded 75% diagnostic accuracy for OH, while the presence of at least one Hypo-ep$^{\Delta 15/24\,h}$ within 90 min after getting up (Hypo-aw$^{\Delta 15/24\,h}$) yielded 93% specificity for OH. A diagnostic accuracy of 87.6% was achieved when including daytime and nighttime ABPM values, weighted BP variability, systolic and diastolic BP loads, nocturnal dipping, and postprandial hypotension in a computerized prediction algorithm. In conclusion, our findings suggest that selected ABPM parameters, such as the number of hypotensive episodes and the presence of awakening hypotension, may be used to screen patients for OH, while using a computerized prediction algorithm that includes all ABPM parameters provides the greatest diagnostic accuracy.

Keywords ABPM · awakening hypotension · hypotensive episodes · orthostatic hypotension

Introduction

Orthostatic hypotension (OH) may affect up to 30% of patients with Parkinson's disease (PD) [1], potentially resulting in dramatic complications, such as falls, fractures, and head trauma, which lead to a significantly increased mortality risk [2–4].

Current diagnostic criteria for OH rely on office blood pressure (BP) measurements demonstrating a drop of at least 20 mmHg (systolic) or 10 mmHg (diastolic) after 3 min of standing from a supine position [5]. Although practical, this definition remains anchored to an "artificial" assessment that only partially recapitulates the full complexity of circadian BP fluctuations occurring during daily living activities [6]. Moreover, these criteria have a limited reproducibility of 79% in neurogenic OH and 67% in non-neurogenic OH [7, 8], with a maximal level of error for BP measurements carried out during the afternoon [9].

Supplementary information The online version of this article (https://doi.org/10.1038/s41440-019-0267-x) contains supplementary material, which is available to authorized users.

✉ Fabrizio Vallelonga
vallelonga.fabrizio@gmail.com

[1] Autonomic Unit and Hypertension Unit, Department of Medical Sciences, University of Turin, via Genova 3, 10126 Turin, Italy

[2] Department of Neuroscience "Rita Levi Montalcini", University of Turin, via Cherasco 15, 10124 Turin, Italy

[3] Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

[4] Department of Electronics and telecommunications, Polytechnic University of Turin, Turin, Italy

Twenty-four hours ambulatory blood pressure monitoring (ABPM) is a validated technique for the ambulatory assessment of arterial blood pressure [10]. Although superior to office blood pressure measurements in essential arterial hypertension [11], the applicability of ABPM in cardiovascular autonomic dysfunction [12] remains limited, and critically, validated criteria for the ABPM detection of OH are still lacking.

We sought to test selected ABPM parameters for the detection of OH and to compare the ambulatory BP profile of PD patients with symptomatic and asymptomatic OH.

Methods

Consecutive patients ($n = 113$) referred to the Autonomic Unit of the Department of Medical Science, University of Torino (Italy), between January 2015 and June 2017 were screened for the following inclusion/exclusion criteria:

Inclusion criteria: Diagnosis of PD per the UK Brain Bank criteria [13]; stable dosage of dopaminergic and vasoactive medications (antihypotensive and/or antihypertensive) for at least 4 weeks prior to inclusion in the study.

Exclusion criteria: Chronic heart failure, chronic renal failure, diabetes mellitus, amyloidosis, autoimmune disorders, malignancies, or other secondary forms of autonomic diseases, diabetes mellitus or diseases potentially associated with autonomic dysfunction [14, 15]. Moderate to severe cognitive impairment, defined as a score lower than 24 in the Montreal Cognitive Assessment. Any atypical features lowering the diagnostic certainty of PD.

Clinical Evaluations

A bedside evaluation of supine and orthostatic BP and ABPM recording were carried out as per the following protocol.

Neurological evaluation

All patients underwent a standard movement disorders neurological examination, including the staging of PD severity as per the Hoehn and Yahr (H&Y) scale [16].

Office blood pressure measurement

Office BP evaluations were always carried out between 2 PM and 5 PM, at least 2 h after a meal, in a standardized environment at a room temperature of 71–75° Fahrenheit. The patients were maintained in a supine position for 10 min and then tilted to a 70-degree upright position for 3 min. BP values were collected in the supine position (average of the last three BP stable measurements) and every minute during the tilt position with an OMRON automatic sphygmomanometer (HEM-9219T-E, Japan ©). OH was defined as a systolic BP drop ≥20 mm Hg or a diastolic BP drop ≥10 mm Hg within 3 min of orthostatic test [5].

Ambulatory Blood Pressure Monitoring

Twenty-four hours ABPMs were performed with a portable device (Spacelabs 90207, Spacelabs Inc., Redmond, WA, USA ©) with appropriate cuff size placed on the non-dominant arm as per the current guidelines [10]. BP measurements were taken every 15 min during the daytime and nighttime. Patients were asked to keep a diary of occupational activities, sleep, and awake time, as well as the time of meals.

Orthostatic hypotension questionnaire

A validated clinical questionnaire - the OH questionnaire (OHQ) [17] – was used to assess OH symptom severity, using the OHQ item 1 to distinguish between "symptomatic" (item 1 ≥ 1) and "asymptomatic" (item 1 = 0) OH.

Outcome measures and definitions

We used normal reference thresholds for ABPM and adhered to the definition of weighted BP variability and dipping patterns proposed by the European Society of Hypertension [10]. BP load was measured as the percentage of BP values higher than normal limits during daytime and nighttime (normal value < 30%). Postprandial hypotension (PPH) was defined as a drop in systolic BP ≥ 20 mmHg within 120 min after the meal, compared to the mean of the last three BP measurements before the meal [18].

Study aims

Our primary aim was to test the diagnostic accuracy of single ABPM-based hypotensive parameters, namely, hypotensive episodes (Hypo-ep) and awakening hypotension (Hypo-aw), in detecting OH. We focused on recordings obtained during the morning hours (between awakening and lunch), which are the most problematic in terms of orthostatic tolerance [19]. Additionally, we prioritized the analysis of systolic BP over a combination of systolic and diastolic BP values to limit the variability in criteria used for the detection of relevant episodes.

For Hypo-ep, we tested the accuracy of the following four criteria:

Systolic BP ≤ 15 mmHg compared to the average 24-hours systolic BP (Hypo-ep$^{\Delta 15/24\,h}$)
Systolic BP ≤ 20 mmHg compared to the average 24-hours systolic BP (Hypo-ep$^{\Delta 20/24\,h}$)
Systolic BP ≤ 15 mmHg compared to the average daytime systolic BP (Hypo-ep$^{\Delta 15/DT}$);
Systolic BP ≤ 20 mmHg compared to the average daytime systolic BP (Hypo-ep$^{\Delta 20/DT}$).

For Hypo-aw, we tested the accuracy of the following four criteria:

At least one Hypo-ep$^{\Delta 15/24\,h}$ occurring within 90 min after getting up in the morning (Hypo-ep$^{\Delta 15/24\,h}$);
At least one Hypo-ep$^{\Delta 15/24\,h}$ occurring within 90 min after getting up in the morning (Hypo-aw$^{\Delta 20/24\,h}$);
At least one Hypo-ep$^{\Delta 15/DT}$ occurring within 90 min after getting up in the morning (Hypo-aw$^{\Delta 15/DT}$);
At least one Hypo-ep$^{\Delta 20/DT}$ occurring within 90 min after getting up in the morning (Hypo-aw$^{\Delta 20/DT}$).

As a secondary aim, we tested the additional diagnostic value provided by a computerized decision algorithm for predicting OH.

Statistical analysis

Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences – version 22 - © 2014 IBM). The normal distribution of continuous variables was tested using the Shapiro–Wilk test. Continuous variables were expressed as the mean ± standard deviation. Qualitative variables were expressed as frequencies or percentage values. Differences between two independent groups were evaluated using Student's t-test for continuous variables with normal distribution and the Mann-Whitney test for continuous variables with non-normal distribution; multiple comparisons (between more than 2 groups) were evaluated with the one-way ANOVA applying Bonferroni's correction for multiple comparisons. Categorical variables were compared using the chi-square test or Fisher's exact test according to the sampling number of analyzed groups. Statistical significance was considered for p values < 0.05.

A prediction analysis was performed with MATLAB R2017b and PYTHON 2.7 using a random forest classification model for the prediction of clinical outcomes [20–22] to analyze which ABPM parameters most accurately detect OH. The model was based on the following logical steps:

a. Definition of latent variables.
b. Definition of outcome.
c. Automated creation of decision trees according to the set rules.
d. Automated categorization of patients according to the created decision trees.
e. Calculation of diagnostic accuracy of the model.

The algorithm created 10 different classification trees with a maximum number of 8 splits for each tree. The prediction (OH presence *vs*. OH absence) was based on the decision of each tree of the forest: if at least 6 of 10 trees of the forest predict the presence of OH, the patient will be classified as OH (+). The accuracy of each variable was estimated through a predictor histogram (Fig. 1). Then, a random labeling method was used to validate the prediction model. In this phase, the algorithm creates a new dataset with randomly assigned outcomes. Then, the random forest model predicts the diagnostic accuracy of the newly assigned outcome. Since the resulting accuracy is expected to be lower than the accuracy of the real dataset, the greater the difference between accuracy on the real dataset vs. the randomly assigned outcome, the greater the performance of the model is.

Results

The study population consisted of 113 patients (81 males and 32 females), with an average age of 64.8 ± 10.2 years (range 34–84), and PD duration of 6.5 ± 4.1 years (range 1–18). There were $n = 15$ patients (13.3%) with H&Y stage 1, $n = 23$ (20.4%) with stage 1.5, $n = 31$ (27.4%) with stage 2, $n = 27$ (23.9%) with stage 2.5, $n = 15$ (13.3%) with stage 3, and $n = 2$ (1.8%) with stage 4. No patients met the clinical criteria of H&Y stage 5. Motor fluctuations were present in $n = 50$ patients (44%) and absent in $n = 63$ (66%). There were 28% patients ($n = 32$) with arterial hypertension and 41% ($n = 46$) in treatment with vasoactive agents: 14% received antihypertensive medication; 11% received antihypotensive medication; and 15% received both antihypertensive and antihypotensive medications. All patients were on treatment with dopaminergic agents for PD, with a levodopa equivalent daily dose (LEDD) of 693 ± 371 mg. No differences related to disease severity [Supplementary Table 1] or vasoactive therapies [Supplementary Table 2] were observed in ABPM outcomes.

OH+ patients ($n = 53$) showed an older age, a higher prevalence of arterial hypertension, and more frequent treatment with antihypotensive drugs than did OH- patients ($n = 60$) [Table 1]. There were no differences in PD duration, disease severity, motor fluctuations, dopaminergic therapies, and antihypertensive medications between the two groups [Table 1].

Office BP measurements showed higher supine BP and lower orthostatic BP in OH+ patients than in OH− patients [Table 1]. Additionally, there were higher nighttime BP

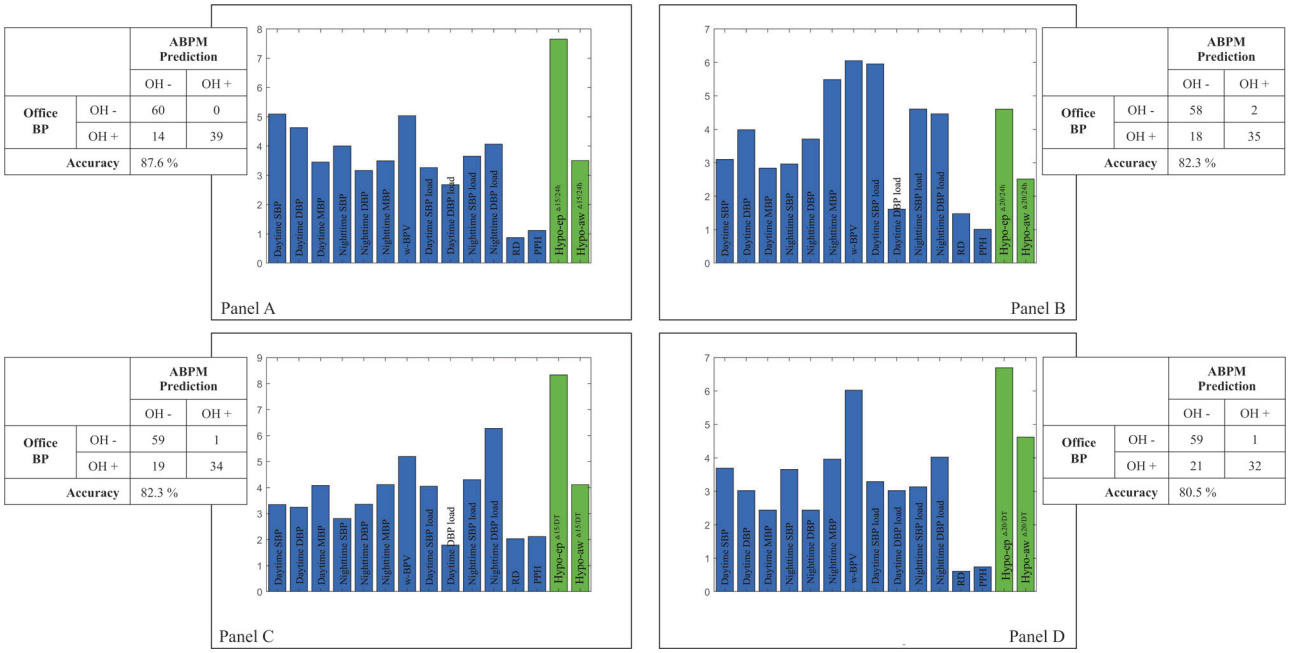

Fig. 1 Prediction analysis with random forest method. A 10-tree random forest was used to predict the presence of OH; four different models were created using the following combinations of ABPM parameters: Hypo-ep$^{\Delta 15/24\,h}$ and Hypo-aw$^{\Delta 15/24\,h}$ (panel A), Hypo-ep$^{\Delta 20/24\,h}$ and Hypo-aw$^{\Delta 20/24\,h}$ (panel B), Hypo-ep$^{\Delta 15/DT}$ and Hypo-aw$^{\Delta 15/DT}$ (panel C), or Hypo-ep$^{\Delta 20/DT}$ and Hypo-aw$^{\Delta 20/DT}$ (panel D), along with standard ABPM parameters. For each model, 2 × 2 tables were used to report accuracy, estimated classification by ABPM parameters, and clinical diagnosis as per in-office BP recording. The histogram represents the normalized predictive performance for each variable (blue: standard parameters; green: hypotensive parameters under investigation). Each classification model was validated through a random-labeling method (see methods section); after randomization of the outcome (presence or absence of OH), the accuracy was 64.6–67.3%; the difference between the accuracy on the randomly assigned outcome dataset and the accuracy on the real dataset (19.9–20.3%) confirmed the reliability of the classification analysis SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; w-BPV: weighted blood pressure variability; RD: reverse dipping pattern; PPH: postprandial hypotension; Hypo-ep: hypotensive episodes; Hypo-aw: awakening hypotension

values, weighted BP variability, and prevalence of nocturnal hypertension and reverse dipping in the former group [Table 2]. Hypo-ep and Hypo-aw detected by ABPM (all four definitions) were more prevalent in OH+ patients than in OH- patients [Table 2], regardless of the symptomatic status [Supplementary Table 3].

There was a strong association between OH (defined as per office BP measurements) and Hypo-ep and Hypo-aw (all four definitions) detected by ABPM [Table 3]. The highest accuracy was found for ≥2 Hypo-ep$^{\Delta 15/24\,h}$ (accuracy 75%, AUC 0.77); the highest specificity (98%) was found for Hypo-aw$^{\Delta 20/DT}$ [Table 3].

A prediction model showed 87.6% accuracy for the diagnosis of OH when combining standard ABPM parameters (daytime and nighttime systolic BP, daytime and nighttime mean BP, daytime and nighttime diastolic BP, weighted BP variability, daytime and nighttime sisto-diastolic BP loads) with Hypo-ep$^{\Delta 15/24\,h}$, Hypo-aw$^{\Delta 15/24\,h}$, reverse dipping pattern, and PPH [Fig. 1 – Panel A]. Number of Hypo-ep$^{\Delta 15/24\,h}$ and weighted-BPV showed the greatest impact in the prediction model (see figure caption). The same analysis was repeated using standard ABPM parameters together with the other ABPM-based hypotensive parameters under investigation (Hypo-ep$^{\Delta 20/24\,h}$ and Hypo-aw$^{\Delta 20/24\,h}$ panel B, Hypo-ep$^{\Delta 15/DT}$ and Hypo-aw$^{\Delta 15/DT}$ panel C, Hypo-ep$^{\Delta 20/DT}$ and Hypo-aw$^{\Delta 20/DT}$ panel D) with lower diagnostic accuracy.

Discussion

We analyzed ABPM-based hypotensive parameters and found that the number of Hypo-ep$^{\triangle 15/24\ h}$ and/or the presence of Hypo-aw$^{\triangle 15/24\ h}$ had the greatest utility in predicting OH. Specifically, having 2 or more episodes of systolic BP drop ≥ 15 mmHg (compared to the average 24-hours ABPM systolic BP values - Hypo-ep$^{\triangle 15/24\ h}$) identified OH with 75% accuracy, 62% sensitivity, and 87% specificity. In addition, an awakening systolic BP drop ≥ 15 mmHg (Hypo-aw$^{\triangle 15/24\ h}$) was associated with 93% diagnostic specificity for OH. The employment of a computerized decisional algorithm further improved the diagnostic accuracy for OH to 87.6%.

These data were proven to be relevant when considering the lack of validated ABPM definitions for both hypotension and awakening hypotension, as well as practical

Table 1 Clinical and demographic characteristics and blood pressure measurements at the orthostatic test

Clinical and Demographic Characteristics			
	OH + *(n = 53)*	OH− *(n = 60)*	*p value*
Age [years]	68 ± 8	62 ± 11	<0.01
Female sex [*n* (%)]	14 (26)	18 (30)	0.67
Weight [kg]	72 ± 12	71 ± 11	0.73
Height [m]	1.69 ± 0.1	1.69 ± 0.1	0.72
Body Mass Index [kg/m^2]	25 ± 3.6	24.6 ± 3.1	0.48
PD duration [years]	7 ± 4	6 ± 4	0.21
Hoehn & Yahr stage 1 [*n* (%)]	6 (11)	9 (15)	0.90
Hoehn & Yahr stage 1.5 [*n* (%)]	10 (19)	13 (22)	0.51
Hoehn & Yahr stage 2 [*n* (%)]	15 (28)	16 (27)	0.82
Hoehn & Yahr stage 2.5 [*n* (%)]	11 (21)	16 (27)	0.63
Hoehn & Yahr stage 3 [*n* (%)]	10 (19)	5 (8)	0.12
Hoehn & Yahr stage 4 [*n* (%)]	1 (2)	1 (2)	0.91
Presence of motor fluctuations [*n* (%)]	27 (51)	23 (38)	0.26
LEDD [mg]	756 ± 403	636 ± 333	0.10
Essential hypertension [*n* (%)]	20 (38)	12 (20)	0.04
Anti-hypertensive drugs [*n* (%)]	4 (8)	12 (20)	0.07
Anti-hypotensive drugs [*n* (%)]	13 (25)	0 (0)	<0.01
Anti-hypotensive plus anti-hypertensive drugs [*n* (%)]	16 (30)	1 (2)	<0.01
Blood pressure measurement at the orthostatic test			
SBP (supine) [mm Hg]	139 ± 18	124 ± 12	<0.01
DBP (supine) [mm Hg]	83 ± 8	76 ± 8	<0.01
SBP (orthostatism 1′) [mm Hg]	111 ± 24	120 ± 15	0.02
DBP (orthostatism 1′) [mm Hg]	71 ± 13	77 ± 9	<0.01
SBP (orthostatism 3′) [mm Hg]	110 ± 20	120 ± 14	<0.01
DBP (orthostatism 3′) [mm Hg]	71 ± 11	77 ± 8	<0.01
Heart rate (supine) [b/min]	73 ± 10	77 ± 12	0.09
Heart rate (orthostatism) [b/min]	82 ± 12	87 ± 14	0.06

OH orthostatic hypotension, *PD* Parkinson's disease, *LEDD* levodopa equivalent daily dose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 2 Ambulatory blood pressure monitoring data

	Ambulatory Blood Pressure Monitoring		
	OH + *(n = 53)*	OH− *(n = 60)*	*p* value
Standard parameters			
Daytime SBP [mm Hg]	120 ± 10.1	122 ± 11.4	0.43
Daytime MBP [mm Hg]	89 ± 7.8	90 ± 8,5	0.26
Daytime DBP [mm Hg]	72 ± 7.3	75 ± 7.7	0.07
Nighttime SBP [mm Hg]	121 ± 14.3	111 ± 13.8	<0.01
Nighttime MBP [mm Hg]	88 ± 10.8	80 ± 10.1	<0.01
Nighttime DBP [mm Hg]	69 ± 10	64 ± 8.8	<0.01
Nocturnal hypertension [*n* (%)]	30 (57)	19 (32)	0.01
Daytime heart rate [b/min]	74 ± 9.1	79 ± 8.9	<0.01
Nighttime heart rate [b/min]	65 ± 8.2	65 ± 9	0.87
Daytime SBP load [%]	21 ± 19.5	19 ± 21.7	0.70
Daytime DBP load [%]	15 ± 14.3	17 ± 19.8	0.47
Nighttime SBP load [%]	46 ± 34.3	24 ± 29.6	<0.01
Nighttime DBP load [%]	43 ± 33	25 ± 27.2	<0.01
Reverse dipping pattern [*n* (%)]	24 (45)	12 (20)	<0.01
High w-BPV [*n* (%)]	36 (68)	25 (42)	0.01
PPH [*n* (%)]	35 (66)	30 (50)	0.09
Hypotensive parameters under investigation			
Hypo-ep $\triangle^{15/24h}$ [*n*]	3.62 ± 3.8	0.80 ± 1.6	<0.01
Hypo-aw$\triangle^{15/24h}$ [*n* (%)]	22 (42)	5 (8)	<0.01
Hypo-ep $\triangle^{20/24h}$ [*n*]	2.57 ± 3.5	0.40 ± 1.1	<0.01
Hypo-aw$\triangle^{20/24h}$ [*n* (%)]	17 (32)	3 (5)	<0.01
Hypo-ep $\triangle^{15/DT}$ [*n*]	3.58 ± 3.5	1.23 ± 1.7	<0.01
Hypo-aw$\triangle^{15/DT}$ [*n* (%)]	22 (42)	4 (7)	<0.01
Hypo-ep $\triangle^{20/DT}$ [*n*]	2.17 ± 2.5	0.58 ± 1.3	<0.01
Hypo-aw$\triangle^{20/DT}$ [*n* (%)]	15 (28)	1 (2)	<0.01

OH orthostatic hypotension, *PD* Parkinson's disease, *LEDD* levodopa equivalent daily dose, *SBP* systolic blood pressure, *MBP* mean blood pressure, *DBP* diastolic blood pressure, *w-BPV* weighted blood pressure variability, *PPH* post-prandial hypotension, *Hypo-ep* hypotensive episode, *Hypo-aw* awakening hypotension

difficulties in performing prolonged orthostatic BP assessment in routine clinical evaluations. Sitting-to-standing BP testing has been proposed as an alternative to the conventional laying-to-standing OH assessment [23], but the concordance with standard BP recording remains suboptimal [24].

The critical importance of hypotension has been demonstrated by the increased risk of adverse outcomes in patients with coronary artery disease and currently relies on office BP measurements < 110/70 mm Hg (systolic/diastolic) [25]. However, this cut-off is not applicable to patients with cardiovascular dysautonomia, and more importantly, validated criteria for the diagnosis of hypotension in a real-life setting are lacking. Some authors proposed using the average 24-hours BP, with a cut-off of 100/60 mmHg (systolic/diastolic) [26], or at least one episode of systolic BP < 100 mmHg [27]. Nonetheless, no studies have tested the accuracy of ABPM for the diagnosis of OH compared to the "conventional" laying-to-standing orthostatic test.

A recent ABPM study proposed repeating a 5-minute standing test four times during the 24-hours recording period [28]. After applying the 20/10 mmHg BP drop criteria (systolic/diastolic), the authors found high sensitivity (82%) and specificity (100%) for the detection of OH with ABPM compared to office BP measurements. Additionally,

Table 3 Diagnostic accuracy of ABPM-based hypotensive parameters in the prediction of orthostatic hypotension

Hypotensive episodes						
Hypo-ep$^{\Delta 15/24\,h}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
≥1 (95% C.I.)	69% (60–77)	/	63% (50–75)	75% (62–86)	65% (56–72)	75% (64–83)
≥2 (95% C.I.)	75% (66–83)	/	87% (75–94)	62% (48–75)	80% (68–89)	72% (65–79)
≥3 (95% C.I.)	72% (62–80)	/	92% (82–97)	49% (35–63)	84% (68–93)	67% (61–73)
N. of episodes (95% C.I.)	/	0.77 (0.68–0.86)	/	/	/	/
Hypo-ep$^{\Delta 20/24\,h}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
≥1 (95% C.I.)	72% (62–80)	/	82% (70–91)	60% (46–74)	74% (62–84)	70% (62–77)
≥2 (95% C.I.)	71% (62–79)	/	93% (84–98)	45% (32–60)	86% (69–94)	66% (60–71)
≥3 (95% C.I.)	65% (56–74)	/	93% (84–98)	34% (22–48)	82% (62–93)	62% (57–66)
N. of episodes (95% C.I.)	/	0.73 (0.64–0.83)	/	/	/	/
Hypo-ep$^{\Delta 15/DT}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
≥1 (95% C.I.)	60% (51–69)	/	42% (29–55)	81% (68–91)	55% (49–61)	71% (57–82)
≥2 (95% C.I.)	69% (60–77)	/	73% (60–84)	64% (50–77)	68% (57–77)	70% (61–77)
≥3 (95% C.I.)	73% (63–81)	/	87% (75–94)	57% (42–70)	79% (65–88)	69% (62–76)
N. of episodes (95% C.I.)	/	0.73 (0.64–0.83)	/	/	/	/
Hypo-ep$^{\Delta 20/DT}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
≥1 (95% C.I.)	65% (56–74)	/	67% (53–78)	64% (50–77)	63% (53–72)	68% (58–76)
≥2 (95% C.I.)	73% (63–81)	/	92% (82–97)	51% (37–65)	84% (69–93)	68% (61–74)
≥3 (95% C.I.)	67% (58–76)	/	95% (86–99)	36% (23–50)	86% (67–95)	63% (58–67)
N. of episodes (95% C.I.)	/	0.71 (0.61–0.81)	/	/	/	/
Awakening hypotension						
Hypo-aw$^{\Delta 15/24\,h}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
Presence (95% C.I.)	69% (60–77)	/	93% (84–98)	42% (28–56)	85% (67–94)	64% (58–69)
Hypo-aw$^{\Delta 15/24\,h}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
Presence (95% C.I.)	65% (56–74)	/	95% (86–99)	32% (20–46)	85% (64–95)	61% (57–66)
Hypo-aw$^{\Delta 15/DT}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
Presence (95% C.I.)	68% (59–77)	/	92% (82–97)	42% (28–56)	81% (64–92)	64% (58–70)
Hypo-aw$^{\Delta 15/DT}$	*Accuracy*	*AUC*	*Specificity*	*Sensitivity*	*PPV*	*NPV*
Presence (95% C.I.)	65% (56–74)	/	98% (91–100)	28% (17–42)	94% (67–99)	61% (57–65)

Hypo-ep hypotensive episode, *Hypo-aw* awakening hypotension, *CI* confidence intervals, *AUC* area under ROC curve, *NPV* negative predictive value, *PPV* positive predictive value

systolic measurements proved to be more sensitive than diastolic measurements [28]. However, the application of this protocol in clinical practice remains limited by two factors. First, some patients may not be able to stand for a long time or to perform BP self-measurements. Second, BP values detected during a laying-to-standing test, although conducted in the patient's home environment, remain somehow artificial and might not reflect BP fluctuations occurring during the activities of daily living.

While the prognostic value of ABPM in arterial hypertension is well known [29–31], the assessment of OH continues to rely on simplistic bedside evaluations [2]. Our findings showed that ABPM might provide additional insights into blood pressure alterations associated with OH, including awakening hypotension, postprandial hypotension, and nocturnal hypertension. Thus, we advocate for the employment of ABPM, to provide additional insights into aspects related to BP fluctuations that might be insufficiently captured at the tilt table testing [6, 32, 33] and to screen PD patients for OH in centers without access to cardiovascular autonomic testing [12]. Additionally, ABPM represents a valid tool to assist point of care in real-life clinical decision making for patients with OH.

While cardiovascular dysautonomia has been traditionally associated with atypical parkinsonism or advanced PD, over 30% of patients enrolled in our study had a H&Y stage lower than 2. This finding is in agreement with previous reports suggesting that cardiovascular dysautonomia may occur early in the course of PD [34] and possibly represents a biomarker of clinical disability [35–39]. Importantly, no

differences related to disease severity were detected in the observed ABPM outcomes.

Among standard ABPM parameters, nocturnal BP values, weighted-BPV, and reverse dipping differed between patients with and without OH. OH is 2–3-fold more frequent in reverse dippers than in dippers [40], and increased nocturnal BP might lead to excessive diuresis with consequent dehydration and awakening hypotension [33]. Additionally, an increased BPV was previously described in patients with OH [41] and orthostatic intolerance [42]. While the present study was not designed to evaluate the diagnostic accuracy of these parameters, we can assume that high nocturnal BP values and 24-hours weighted BPV are more likely to be associated with OH. These data seem to be confirmed by the greater accuracy of the random forest analysis, which takes into consideration the additional contribution provided by conventional ABPM-based parameters, such as nocturnal BP and BPV.

Proposed criteria for the diagnosis of Orthostatic Hypotension through ABPM

We suggest introducing Hypo-ep$^{\Delta 15/24\,h}$ and Hypo-aw$^{\Delta 15/24\,h}$ as new hypotensive parameters for the diagnosis of OH using one of the following criteria:

- Two or more Hypo-ep$^{\Delta 15/24\,h}$ (accuracy 75%, positive predictive value 80%).
- Presence of Hypo-aw$^{\triangle 15/24\ h}$ (accuracy 69%, positive predictive value 85%).

These criteria would be simply and promptly applicable in clinical practice by observing the BP measurements present in the ABPM report. Greater diagnostic accuracy (87.6%) can be achieved using the random forest decisional analysis, which uses a wide range of ABPM parameters (daytime systolic BP, daytime diastolic BP, daytime mean BP, nighttime systolic BP, nighttime diastolic BP, nighttime mean BP, weighted-BPV, daytime systolic and diastolic BP load, nighttime systolic and diastolic BP load, presence/absence of reverse dipping pattern, presence/absence of postprandial hypotension, number of Hypo-ep$^{\triangle 15/24\ h}$ and presence/absence of Hypo-aw$^{\triangle 15/24\,h}$) (online tool available at the following link: https://github.com/ABurrello/OH-detection-by-ABPM/archive/master.zip).

Perspectives

With the simple evaluation of Hypo-ep$^{\triangle 15/24\ h}$ and Hypo-aw$^{\triangle 15/24\,h}$, independently from the random forest algorithm, our population was divided into 44% of patients ($n = 50$) without OH and 31% ($n = 35$) with OH both during office and ABPM evaluations, 9% ($n = 10$) with OH only at the ambulatory evaluation, and 16% ($n = 18$) with OH only at the office evaluation. Additional studies are needed to clarify whether the hypotensive episodes detected with ABPM, but not during orthostatic testing (9% of our cohort) or office OH not associated with significant ABPM alterations (16% of our cohort), should be considered false negatives/positives or whether one of the two techniques is superior to the other in the detection of OH. Different mechanisms might be involved in the control of blood pressure during tests of "functional capacity," such as the tilt table, compared to tests of "functional activity," such as the 24-hours ABPM. Another hypothesis is that ABPM might be more sensitive than "conventional" autonomic testing in capturing delayed-OH, a frequently underdiagnosed yet disabling autonomic disorder. Given the need for additional studies confirming and validating these hypotheses, we hypothesize a wider spectrum of clinical applications for ABPM within the field of cardiovascular autonomic disorders.

Study Limitations

Some critical factors should be considered in the interpretation of our findings. First, we enrolled patients regardless of their treatment with vasoactive medications. In fact, our aim was to provide a "real-life" assessment of blood pressure fluctuations without excluding the significant percentage of patients with cardiovascular dysautonomia that usually receive treatment with antihypotensive and antihypertensive medications. Second, we tested the accuracy of several yet not unlimited ABPM cut-off values. While adhering to BP cut-off criteria in line with common clinical practice, we cannot exclude the possibility that intermediate BP values (e.g., 18 mmHg) not included in our analyses might provide more accurate results. Additionally, we prioritized systolic BP over a combination of systolic and diastolic BP values. This choice was supported by previous findings demonstrating that systolic measurements have higher sensitivity than diastolic measurements in the detection of OH with ABPM [28]. Third, we could not evaluate the association of ABPM parameters with delayed OH, which is a frequently underdiagnosed yet disabling condition. Future studies will need to clarify the sensitivity of ABPM in detecting blood pressure changes occurring over head-up tilt testing longer than 3 min. Finally, while this study focused on correlations between OH measured during the head-up tilt test and 24-hours ABPM in an ecologically valid environment, a more detailed characterization of autonomic dysfunction using sudomotor testing and a clinical assessment of autonomic symptoms with validated clinical scales would provide additional insights into the pathophysiology of the observed outcomes.

Conclusions

Our data support the employment of ABPM in patients with suspected dysautonomia and propose two specific parameters for the ambulatory screening of OH with ABPM: a) number of hypotensive episodes, defined as a systolic BP drop ≥ 15 mmHg, compared to the average 24-hours systolic BP; and b) recording of awakening hypotension, defined as a systolic BP drop ≥ 15 mmHg within 90 min after getting up in the morning compared to the average 24-hours systolic BP.

Compliance with ethical standards

Conflict of interest AR received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco and UCB Pharma. AM is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL Behring, Cynapsus Therapeutics, and UCB Pharma. He has received grant support from Lundbeck and from Abbott. MZ received speaker and/or consulting honoraria from Medtronic, Lundbeck, UCB Pharma and AbbVie. AM received speaker and/or consulting honoraria from AMGEN and Boheringer (Advisory Board). The remaining authors declare that they have no conflict on interest.

References

1. Merola A, Sawyer RP, Artusi CA, Suri R, Berndt Z, Lopez-Castellanos JR, et al. Orthostatic hypotension in Parkinson disease: Impact on health care utilization. Park Relat Disord. 2018;47:45–9.
2. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. Eur Heart J. 2015;36:1609–17.
3. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. J Am Coll Cardiol. 2015;66:848–60.
4. Romagnolo A, Zibetti M, Merola A, Canova D, Sarchioto M, Montanaro E, et al. Cardiovascular autonomic neuropathy and falls in Parkinson disease: a prospective cohort study. J Neurol. 2019;266:85–91.
5. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21:69–72.
6. Norcliffe-Kaufmann L, Kaufmann H. Is ambulatory blood pressure monitoring useful in patients with chronic autonomic failure? Clin Auton Res. 2014;24:189–92.
7. Belmin J, Abderrhamane M, Medjahed S, Sibony-Prat J, Bruhat A, Bojic N, et al. Variability of blood pressure response to orthostatism and reproducibility of the diagnosis of orthostatic hypotension in elderly subjects. J Gerontol A Biol Sci Med Sci. 2000;55:M667–71.
8. Vara-Gonzalez L, Arauzo Alonso S, Gonzalez Fernandez RM, Marin-Gil Vecilla M, Virseda Marin N, Munoz Cacho P. Reproducibility of postural changes of blood pressure in hypertensive elderly patients in primary care. Blood Press Monit. 2006;11:17–20.
9. Ward C, Kenny RA. Reproducibility of orthostatic hypotension in symptomatic elderly. Am J Med. 1996;100:418–22.
10. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. Variability ESoHWGoBPMaC. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014;32:1359–66.
11. Trazzi S, Mutti E, Frattola A, Imholz B, Parati G, Mancia G. Reproducibility of noninvasive and intra-arterial blood pressure monitoring: implications for studies on antihypertensive treatment. J Hypertens. 1991;9:115–9.
12. Milazzo V, Di Stefano C, Vallelonga F, Sobrero G, Zibetti M, Romagnolo A, et al. Reverse blood pressure dipping as marker of dysautonomia in Parkinson disease. Park Relat Disord. 2018;56:82–7.
13. Gibb WR. Accuracy in the clinical diagnosis of parkinsonian syndromes. Post Med J. 1988;64:345–51.
14. Dineen J, Freeman R. Autonomic neuropathy. Semin Neurol. 2015;35:458–68.
15. Mathias CJ. Autonomic diseases: clinical features and laboratory evaluation. J Neurol Neurosurg Psychiatry. 2003;74(Suppl 3):31–41.
16. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a baseline analysis of the DATATOP cohort. The Parkinson Study Group. Neurology. 1990;40:1529–34.
17. Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res. 2012;22:79–90.
18. Jansen RW, Connelly CM, Kelley-Gagnon MM, Parker JA, Lipsitz LA. Postprandial hypotension in elderly patients with unexplained syncope. Arch Intern Med. 1995;155:945–52.
19. Shibao C, Lipsitz LA, Biaggioni I. ASH position paper: evaluation and treatment of orthostatic hypotension. J Clin Hypertens. 2013;15:147–53.
20. Yang Y, Burrello J, Burrello A, Eisenhofer G, Peitzsch M, Tetti M, et al. Classification of microadenomas in patients with primary aldosteronism by steroid profiling. J Steroid Biochem Mol Biol. 2019. https://doi.org/10.1016/j.jsbmb.2019.01.008.
21. Baldassano SN, Brinkmann BH, Ung H, Blevins T, Conrad EC, Leyde K, et al. Crowdsourcing seizure detection: algorithm development and validation on human implanted device recordings. Brain. 2017;140:1680–91.
22. Lebedev AV, Westman E, Van Westen GJ, Kramberger MG, Lundervold A, Aarsland D, et al. Random Forest ensembles for detection and prediction of Alzheimer's disease with a good between-cohort robustness. Neuroimage Clin. 2014;6:115–25.
23. Gorelik O, Cohen N. Seated postural hypotension. J Am Soc Hypertens. 2015;9:985–92.
24. Breeuwsma AC, Hartog LC, Kamper AM, Groenier KH, Bilo HJ, Kleefstra N, et al. Standing orthostatic blood pressure measurements cannot be replaced by sitting measurements. Hypertens Res. 2017;40:765–70.
25. Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP. What is the optimal blood pressure in patients after acute coronary syndromes? Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation. 2010;122:2142–51.
26. Divison-Garrote JA, Banegas JR, De la Cruz JJ, Escobar-Cervantes C, De la Sierra A, Gorostidi M, et al. Hypotension based on office and ambulatory monitoring blood pressure. Prevalence and clinical profile among a cohort of 70,997 treated hypertensives. J Am Soc Hypertens. 2016;10:714–23.
27. Scuteri A, Modestino A, Frattari A, Di Daniele N, Tesauro M. Occurrence of hypotension in older participants. Which 24-hour

ABPM parameter better correlate with? J Gerontol A Biol Sci Med Sci. 2012;67:804–10.
28. Vichayanrat E, Low DA, Iodice V, Stuebner E, Hagen EM, Mathias CJ. Twenty-four-hour ambulatory blood pressure and heart rate profiles in diagnosing orthostatic hypotension in Parkinson's disease and multiple system atrophy. Eur J Neurol. 2017;24:90–7.
29. Fagard RH, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Prognostic significance of ambulatory blood pressure in hypertensive patients with history of cardiovascular disease. Blood Press Monit. 2008;13:325–32.
30. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, et al. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the ambulatory blood pressure collaboration in patients with hypertension (ABC-H) Meta-Analysis. Hypertension. 2016;67:693–700.
31. Pierdomenico SD, Pierdomenico AM, Di Tommaso R, Coccina F, Di Carlo S, Porreca E, et al. Morning blood pressure surge, dipping, and risk of coronary events in elderly treated hypertensive patients. Am J Hypertens. 2016;29:39–45.
32. Gibbons CH, Schmidt P, Biaggioni I, Frazier-Mills C, Freeman R, Isaacson S, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol. 2017;264:1567–82.
33. Vallelonga F, Maule S Diagnostic and therapeutical management of supine hypertension in autonomic failure: a review of the literature. J Hypertens. 2018. https://doi.org/10.1097/HJH.0000000000002008.
34. Liepelt-Scarfone I, Pilotto A, Muller K, Bormann C, Gauss K, Wurster I, et al. Autonomic dysfunction in subjects at high risk for Parkinson's disease. J Neurol. 2015;262:2643–52.
35. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, et al. Autonomic dysfunction in Parkinson's disease: a prospective cohort study. Mov Disord. 2018;33:391–7.
36. De Pablo-Fernandez E, Warner TT. Autonomic dysfunction in parkinson's disease: the hidden game changer? Mov Disord. 2018;33:1028.
37. Merola A, Romagnolo A, Lopiano L, Espay AJ. Reply to: "autonomic dysfunction in Parkinson's disease: tthe hidden game changer?". Mov Disord. 2018;33:1028–9.
38. De Pablo-Fernandez E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of parkinson disease. JAMA Neurol. 2019. https://doi.org/10.1001/jamaneurol.2018.4377.
39. Merola A, Romagnolo A, Comi C, Rosso M, Artusi CA, Zibetti M, et al. Prevalence and burden of dysautonomia in advanced Parkinson's disease. Mov Disord. 2017;32:796–7.
40. Fagard RH, De Cort P. Orthostatic hypotension is a more robust predictor of cardiovascular events than nighttime reverse dipping in elderly. Hypertension. 2010;56:56–61.
41. Tabara Y, Matsumoto T, Murase K, Setoh K, Kawaguchi T, Nagashima S, et al. Day-to-day home blood pressure variability and orthostatic hypotension: the Nagahama Study. Am J Hypertens. 2018;31:1278–85.
42. Sunwoo JS, Yang TW, Kim DY, Lim JA, Kim TJ, Byun JI, et al. Association of blood pressure variability with orthostatic intolerance symptoms. PLoS One. 2017;12:e0179132.