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Reverse Blood Pressure Dipping as Marker of Dysautonomia in Parkinson Disease

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ABSTRACT

Introduction: We sought to evaluate if the presence of abnormal circadian loss of nocturnal blood pressure dipping (reverse dipping) is associated with cardiovascular dysautonomia, a major source of morbidity in Parkinson disease.

Methods: Consecutive Parkinson disease patients were enrolled in this cross-sectional study between January 2015 and June 2017. All subjects underwent same-day autonomic testing and 24-hour ambulatory blood pressure monitoring. Cardiovascular dysautonomia was defined by the presence of at least one moderate or severe cardiovagal and adrenergic test abnormality.

Results: We recruited 114 PD patients (79 males; mean age 64 ± 10 years; disease duration 6 ± 4 years). Cardiovascular dysautonomia was present in 32% (36/114). The blood pressure patterns were normal dipping in 28.9% (n= 33), extreme dipping in 6.1% (n= 7), reduced dipping in 32.5% (n= 37), and reverse dipping in 32.5% (n= 37). Reverse dipping was disproportionately prevalent in subjects with cardiovascular dysautonomia (69% vs 15%, $p< 0.001$). The diagnostic accuracy of reverse dipping in discriminating cardiovascular dysautonomia (AUC 0.791, specificity 84%, sensitivity 69%) was higher than that of bedside blood pressure ascertainment of neurogenic orthostatic hypotension (0.681, 66%, 69%) and supine hypertension (0.641, 78%, 50%).

Conclusions: Reverse nocturnal blood pressure dipping is a marker of cardiovascular dysautonomia in Parkinson disease, which can be screened for with ease and affordability using ambulatory blood pressure monitoring.

INTRODUCTION

Cardiovascular dysautonomia is a frequent yet overlooked complication of Parkinson disease (PD). In healthy individuals, baroreflex responses to postural changes maintain a constant blood pressure (BP) and cerebral perfusion regardless of positional changes. Alterations of this autonomic compensatory mechanism, which involves the synchronized activity of the sympathetic and parasympathetic systems,[1,2] may result in alternating orthostatic hypotension and supine hypertension during daytime and loss or reversion of the normal fall in BP during sleep ("reduced dipping" and "reverse dipping").[3] The disruption in BP control is compounded by an exaggerated hypotensive response to meals, physical exercise, dehydration, and high ambient temperatures.[4,5,6]

Whereas *reduced dipping* is a non-specific BP pattern influenced by several unrelated clinical variables (e.g., sleep disorders, hypertension, etc.), *reverse dipping* is a recognized phenomenon in PD, with direct effects associated with worsening nocturnal supine hypertension and indirect effects via worsening daytime orthostatic hypotension.[4,5,7] It is unclear the extent to which it reflects cardiovascular dysautonomia, as detected by conventional autonomic testing.[8] In this study, we sought to evaluate whether reverse dipping as measured by a simple 24-hour ambulatory BP monitoring device, is associated with, and could serve as marker for, cardiovascular dysautonomia in patients with PD.

METHODS

Study population

Consecutive patients referred to the Movement Disorder Clinic of the Department of Neuroscience, University of Torino (Italy) between January 2015 and June 2017 were invited to participate in this study.

Inclusion criteria. We recruited patients meeting UK Brain Bank criteria for idiopathic PD[9] for at least 2 years from symptom onset, aged between 18 and 85 years old, on stable dosage of dopaminergic medications, anti-hypertensive medications, or alpha-blockers for prostate hypertrophy (if applicable) for at least 4 weeks prior to recruitment.

Exclusion criteria. We excluded subjects with previous diagnosis of neurogenic orthostatic hypotension, on treatment with vasopressor agents including, but not limited to, midodrine, fludrocortisone, and prostigmine; or with the following comorbidities: diabetes mellitus or other diseases potentially associated with dysautonomia,[10] cardiac dysrhythmia, cognitive impairment (mini mental state examination < 24/30), renal failure, heart disease, and obstructive sleep apnea syndrome.

The study was approved by the Ethics Committee of the "Città della Salute e della Scienza" Hospital, Turin, and all patients provided written informed consent.

Cardiovascular Autonomic Testing

All patients underwent a standardised battery of cardio-vagal and adrenergic tests (DAN Test Microlab, Padua, Italy), as per the following protocol:

(1) Analysis of the heart rate (HR) variability during deep breathing: The R-R interval was continuously recorded while the subject was asked to breathe deeply and evenly at 6 breaths/min. Expiratory to inspiratory HR variability was calculated from the maximum and minimum R-R interval during five consecutive breathing cycles.

(2) Analysis of BP fluctuations and HR variability during the Valsalva maneuver: subjects were asked blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg,

holding the pressure for 15 sec. The Valsalva ratio was calculated as the ratio between the longest R-R interval (shortly after the maneuver) and the shortest R-R interval (during the strain period). BP changes of Valsalva manoeuvre were measured as the fall in BP during early phase II, the increase in BP during late phase II, the overshoot of BP during phase IV, and the recovery time after phase III.[11]

(3) Analysis of BP and HR response during tilt-up: Subjects were initially positioned supine on the table held in the horizontal position for 10 minutes, then tilted to a 60° upright position for at least 5 minutes. BP and HR were constantly monitored during the entire duration of the test using both a beat-to-beat BP monitor (Finapres; Finapres Medical Systems B.V., The Netherlands) and confirmed by manual sphygmomanometer BP recordings after 1, 3, and 5 minutes of standing.

After adjusting for age, the cardiovascular autonomic tests were scored as follows:

Cardio-vagal Index: 0= normal; 1= reduction in deep-breathing HR variability < 50%; 2= reduction in the deep-breathing HR variability > 50% or reduced baroreflex sensitivity index; 3= reduction in deep-breathing HR variability > 50% and reduced baroreflex sensitivity index.[11]

Adrenergic Index: 0= normal; 1= reduced late phase II and/or mildly increased BP recovery time (5-6 second) and/or absent phase IV during the Valsalva manoeuvre; 2= moderately increased BP recovery time (7-10 seconds) during the Valsalva manoeuvre; 3= markedly increased BP recovery time (> 10 seconds) and/or absent late phase II and phase IV during the Valsalva manoeuvre; 4= above plus orthostatic hypotension.[11] Cases with uncertain adrenergic response were also assessed with the sustained hand-grip test, measuring the diastolic BP response during isometric muscle contraction (squeezing a handgrip dynamometer for 5 minutes at one-third of the previously evaluated maximal effort). Results were considered normal (score= 0) when diastolic BP increased by at least 15 mmHg; borderline (score= 1) between 15 and 10 mmHg; and abnormal (score= 3) when lower than 10 mmHg.[12]

Cardiovascular dysautonomia was defined as a moderate to severe alteration in at least one cardio-vagal and one adrenergic test, with a total score ≥ 4.[11] Orthostatic hypotension was defined as a reduction of systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg within three minutes of standing. We defined neurogenic orthostatic hypotension (nOH) as the presence of orthostatic hypotension in combination with cardiovascular dysautonomia; non neurogenic orthostatic hypotension (OH) the presence of orthostatic hypotension with normal cardio-vagal and adrenergic tests.[13] Supine hypertension was defined as supine systolic BP ≥ 150 mmHg or diastolic BP ≥ 90 mmHg.[14]

All subjects were evaluated during their best ON state, defined as a period of perceived maximal efficacy of dopaminergic medications and at least 3 hours after the last meal. Examinations were performed in a silent room, maintained at ambient temperature (23°C–26°C). Data were compared to normative age-adjusted stratified data (control values based on Autonomic Unit database and standard recommendations[15]).

Dopaminergic medications were logged and the levodopa equivalent daily dose (LEDD) was calculated according to the conversion table proposed by Tomlison et al.[16]

Ambulatory Blood Pressure Monitoring

The ambulatory BP monitoring was performed using a Spacelabs 90207 (Spacelabs™ Medical, WA, USA) for 24 consecutive hours (from 5:00 PM of day 1 to 5:00 PM of day 2) recording BP values every 15 minutes. The appropriate cuff size was selected according to the current guidelines.[17] A difference of < 5 mm Hg between 3 ambulatory BP measurements and 3 auscultatory readings simultaneously obtained was ensured before the recording.

Patients were asked to keep a diary to correlate BP values to daily activities, position, and symptoms, and to use the device for at least 1.75 hours during the night, which is considered the minimal threshold for a reliable 24-hour ambulatory BP monitoring.[17] Daytime and night-time were

defined by patient diary. BP load was measured as the percentage of BP values higher than normal limits during daytime and night-time (normal value < 30%).[18]

Nocturnal Dipping, Reduced Dipping, and Reverse Dipping

Mean systolic and diastolic values for daytime and night-time BP and the difference between daytime and night-time mean values were calculated. The dipping pattern, corresponding to the average reduction in systolic BP between waking hours and sleep, was classified as per the recommendations of the European Society of Hypertension[19] as follows:

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

Statistical analysis

Sample size calculation. We used published data reporting a mean day-to-night systolic BP difference of 6%, with a standard deviation of 10%.[20] Using these data, we estimated that a sample size of 100 patients would have sufficed to detect significant differences in PD patients with and without cardiovascular dysautonomia, with 80% power at the 5% level of significance (Hintze J. PASS 12. NCSS, LLC 2013. Kaysville, Utah, USA). The recruitment goal was set at 130 patients, accounting for a 20% rate of drop-out or tests with insufficient technical quality for accurate interpretation.

Continuous variables were expressed as mean ± standard deviation or median and inter-quartile range as appropriate. Qualitative variables were expressed as absolute values of frequency and percentage values. Normal distribution of variables was tested using the Kolgorov-Smirnov and residual analysis tests. Differences between independent groups were evaluated using a t-test for continuous variables with normal distribution and the Mann-Whitney or Kruskal-Wallis test for continuous variables with non-normal distribution. Categorical variables were compared using the chi-square test. Correlation between variables was measured with Pearson's correlation coefficients. Then, to evaluate the relative risk of cardiovascular dysautonomia in patients with reverse dipping, a binary logistic regression model was applied, using dysautonomia as a dependent variable, and reverse dipping, age, sex, disease duration, hypertension, and anti-hypertensive medications as independent variables. The diagnostic accuracy of ambulatory BP monitoring parameters in distinguishing patients with and without cardiovascular dysautonomia was estimated using Receiver Operating Characteristic (ROC) curves. The area under the ROC curve, sensitivity, specificity, positive predictive value, and negative predictive value for different cut-offs of systolic day-to-night difference in BP (corresponding to BP patterns) were calculated. Statistical significance was considered for p values < 0.05. Statistical analysis was performed with software packages R Studio (version 0.98.978 - © 2009-2013 RStudio) and SPSS (Statistical Package for the Social Sciences – version 22 - © 2014 IBM).

RESULTS

Of 130 patients screened, 11 met one or more exclusion criteria, 3 could not wear the ambulatory BP monitor due to severe dyskinesia or tremor, and 2 could not complete all of the autonomic testing; 114 (79 males and 35 females) met all inclusion and none of the exclusion criteria and were recruited into the study. The mean age was 64 ± 10 years (range 34-84), with a mean PD duration of 6 ± 4 years (range 2-18) (Table 1).

Cardiovascular dysautonomia and BP patterns. One third of the cohort met criteria for cardiovascular dysautonomia (32%, 36/114). A sympathetic pattern of dysautonomia was present in 11 (30%), a parasympathetic pattern in 10 (28%), and a mixed pattern in 15 (42%). Sixty-nine percent of the subjects had nOH, 33% OH. Supine hypertension was also more prevalent in patients with than without dysautonomia (50% vs. 22%). Bedside supine BP values were higher in patients with than without OH (139±16/82±7 vs 126±13/76±8 mmHg, $p<0.001$).

The mean 24-hour BP was 121±10 / 72±7 mmHg (systolic/diastolic), with normal dipping pattern in 28.9% (n=33), extreme dipping in 6.1% (7), reduced dipping in 32.5% (37), and reverse dipping in 32.5% (37). Reverse dipping (Figure 1) was disproportionately prevalent in patients with cardiovascular dysautonomia compared to those without (69% vs 15%, $p<0.001$). Patients' diary showed no difference in quality/duration of sleep between PD patients with and without autonomic neuropathy. The mean number of nighttime BP readings was 26±6. Only 6 patients had low quality ambulatory BP monitoring (<70% of expected measurements) but were included in the study since BP patterns were still identifiable.

Reverse dipping and cardiovascular dysautonomia. Night-time BP values were significantly higher in patients with cardiovascular dysautonomia (Table 1). The systolic and diastolic day-to-night BP difference correlated with the severity of cardiovascular dysautonomia (R -0.448, $p<0.001$, systolic; R -0.424, $p<0.001$, diastolic). In addition, logistic regression analysis showed a strong association between reverse dipping and cardiovascular dysautonomia (OR 9.62, 95% CI 3.41-27.14, $p<0.001$), after adjusting for age, sex, disease duration, comorbid essential hypertension, and anti-hypertensive medications.

Diagnostic performance. Systolic and diastolic day-to-night BP difference discriminated cardiovascular dysautonomia with an area under the curve of 0.791 and 0.783 (Table 2; Figure 2), respectively. Reverse dipping discriminated cardiovascular dysautonomia with 80% accuracy, 84% specificity, and 69% sensitivity. We additionally calculated the capacity to discriminate cardiovascular dysautonomia for nOH, supine hypertensione, and the combined score "reverse dipping plus nOH". The area under the curve, specificity and sensitivity were as follows: 0.681, 66% and 69% for nOH; 0.641, 78% and 50% for supine hypertension; and 0.724, 95% and 50% for the combined score "reverse dipping plus nOH". Reverse dipping discriminated nOH with an area under the curve of 0.689 (systolic day-to-night BP difference) and 0.672 (diastolic day-to-night BP difference), with 61% accuracy, 76% specificity, and 43% sensitivity.

DISCUSSION

We found that reverse BP dipping is present in a third of patients with PD and is robustly associated with cardiovascular dysautonomia, independently from age, sex, disease duration, comorbid essential hypertension, and intake of antihypertensive medications. Furthermore, ambulatory BP monitoring data yields 80% accuracy, 84% specificity, and 69% sensitivity for the diagnosis of cardiovascular dysautonomia as compared to laboratory-based autonomic tests as the gold standard. Compared with nOH and the combined score "reverse dipping plus nOH", reverse dipping was most sensitive and accurate in discriminating cardiovascular dysautonomia, with an area under the receiver operator curve of 0.791 for the systolic and 0.783 for the diastolic day-to-night BP difference.

The disruption of cardiovascular homeostasis in PD is a complex phenomenon based on at least three different mechanisms, namely cardiac noradrenergic sympathetic denervation, central and peripheral norepinephrine deficiency, and arterial baroreflex failure.[7,21] While these autonomic mechanisms can be tested in specialized laboratories, the advanced level of training and the amount

of time required for the execution and interpretation of data inevitably limit the availability of neurophysiological autonomic examination.[7,8] Still, the diagnosis and treatment of cardiovascular dysautonomia, with a prevalence of over 30% in PD, remain critical to reduce the risk of associated complications such as falls, brain hemorrhage, and fractures.[22] The 24-hour ambulatory BP monitoring represents an accessible technology, extensively validated for the assessment of chronic hypertension.[18]

Although the high correlation between reverse dipping and the presence of dysautonomia does not imply causation, our results identified reverse dipping as a marker of dysautonomia. The association between reverse dipping and cardiovascular dysautonomia has been recognized in PD and other disorders. PD patients with a reduced or reverse pattern on 24h ambulatory BP monitoring had been reported to have higher prevalence of orthostatic hypotension, but correlation with autonomic symptoms was uncertain (no autonomic tests were performed).[23] A study investigating the circadian rhythm of BP in patients with type-1 diabetes found that reverse dipping predicts dysautonomia with high diagnostic accuracy.[24] Ambulatory BP monitoring has served to screen for complications related to cardiovascular dysautonomia, such as cardiomyopathy,[20] renal impairment,[25] and cerebrovascular disorders,[26] but never previously for the diagnosis of cardiovascular dysautonomia of PD. The ability of 24-hour ambulatory BP monitoring to detect dysautonomia with greater accuracy than bedside measurement of orthostatic hypotension is even more relevant when considering that only 50% of patients with orthostatic hypotension endorse postural lightheadedness when using the Orthostatic Hypotension Questionnaire[27] and that bedside BP measurements inadequately recapitulate the full complexity of hemodynamic changes occurring during normal activities throughout the day and night. Our results support the finding of reverse dipping as a marker of dysautonomia, considered by other authors[7] the main contributor of supine hypertension.

Several limitations temper the strength of our conclusions. First, PD is frequently associated with sleep disturbances, which might contribute to alterations in the physiology of nocturnal dipping. While we did not observe any significant differences in the quality of sleep from patients with and without cardiovascular dysautonomia, as per their ambulatory diary (data not shown), an effect of sleep disorders on the circadian BP rhythm cannot be excluded. Second, there was a significant difference in L-dopa and dopamine agonists LEDD between patients with and without dysautonomia. While this finding may simply reflect the fact that dysautonomia is associated with a more advanced phase of PD, we may not exclude a differential contribution of each dopaminergic treatment in some of the observed results. Third, 29% of the patients were under therapy acting on BP (antihypertensive and/or alpha-blockers for prostate hypertrophy). Indeed the study was intended to be "real life" and stable treatments were not discontinued to avoid a disruption of hemodynamic balance. Reverse dipping, however, discriminated cardiovascular dysautonomia with similar AUCs in both subgroups of patients, with and without vasoactive therapy (data not shown) suggesting ambulatory BP monitoring can have a similarly optimal diagnostic capacity regardless of the presence of vasoactive therapies. Lastly, the cut-off used for the diagnosis of orthostatic hypotension was the conventional reduction in systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg within three minutes of standing rather than the more stringent, higher cut-off values (30/15 mmHg) as recently suggested.[28]

CONCLUSIONS

This study confirms the alterations in circadian BP rhythm in PD and supports the ascertainment of reverse dipping as marker of cardiovascular dysautonomia with 80% accuracy, 84% specificity, and 69% sensitivity. For the ascertainment of reverse dipping in PD, 24-hour ambulatory BP monitoring represents an easy and affordable screening tool, with a higher diagnostic accuracy than nOH and the combined score "reverse dipping plus nOH".

AUTHOR CONTRIBUTIONS

Conception and design of the study: VM, CDS, FV, GS, MZ, AME, LL, FV, SM

Acquisition and analysis of data: VM, CDS, FV, GS, AR, AE, SM

Drafting a significant portion of the manuscript or figures: VM, MZ, AR, AME, AMI, AE, LL, FV, SM

All Authors fulfilled the Authorship criteria and approved the final version of the article. All gave agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The order of authors listed in the manuscript has been approved by all of them.

CONFLICTS OF INTEREST

Dr. Milazzo nothing to report.

Dr. Di Stefano nothing to report.

Dr. Vallelonga nothing to report.

Dr. Sobrero nothing to report.

Dr. Zibetti received speaker and/or consulting honoraria from Medtronic, Lundbeck, UCB Pharma and AbbVie.

Dr. Romagnolo received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco and UCB Pharma.

Dr. Merola is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL Behring, Cynapsus Therapeutics, and UCB Pharma.

Dr. Milan received speaker and/or consulting honoraria from AMGEN and Boheringer (Advisory Board).

Prof. Espay has received grant support from the NIH, Great Lakes Neurotechnologies and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member

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Prof. Lopiano received honoraria for lecturing and travel grants from Medtronic, UCB Pharma and AbbVie.

Prof. Veglio nothing to report.

Dr. Maule nothing to report.

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Nothing to report.

DATA ACCESS, RESPONSIBILITY AND ANALYSIS STATEMENT

V. Milazzo and S. Maule had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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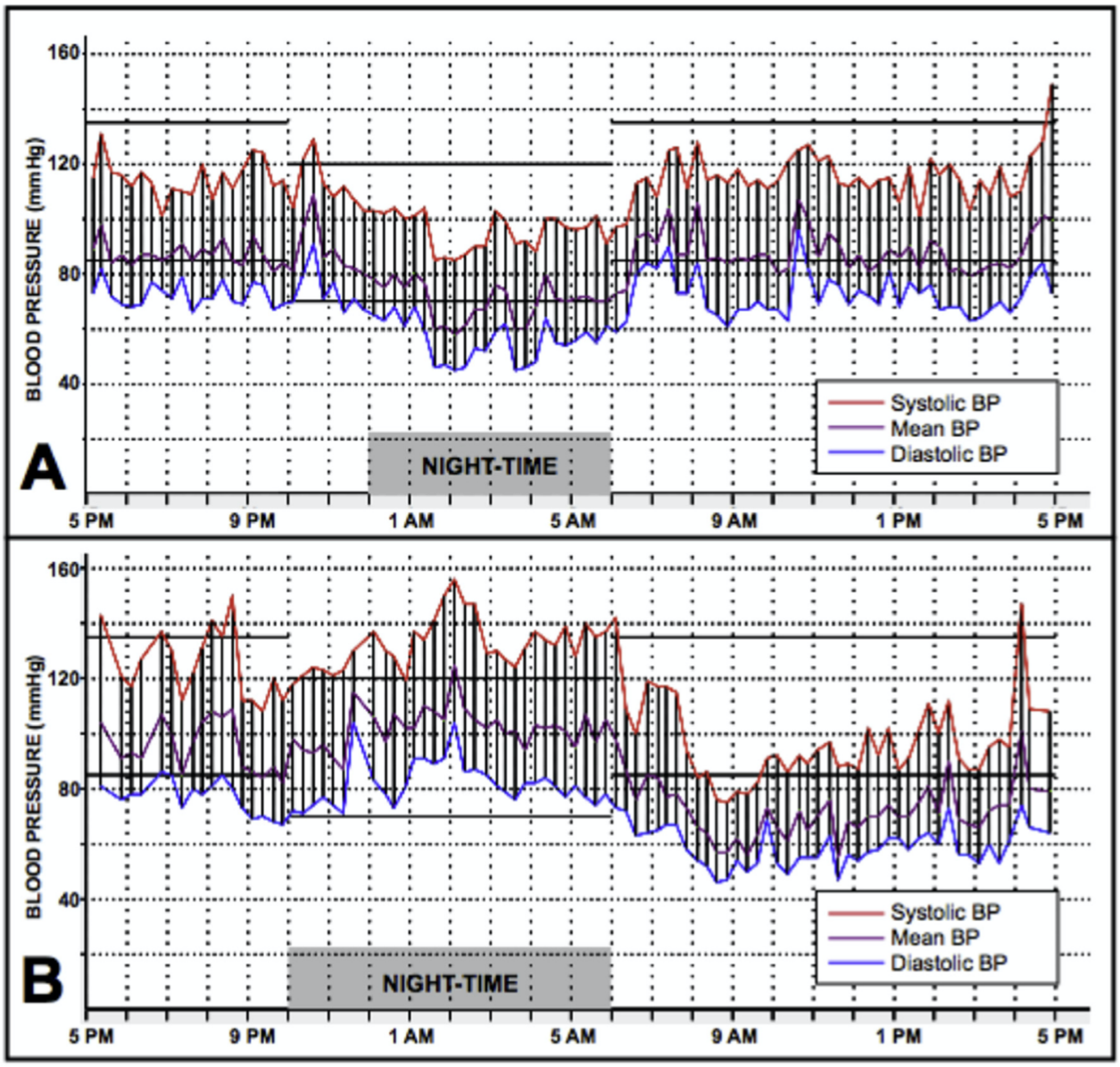
FIGURE 1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5 PM

FIGURE 2

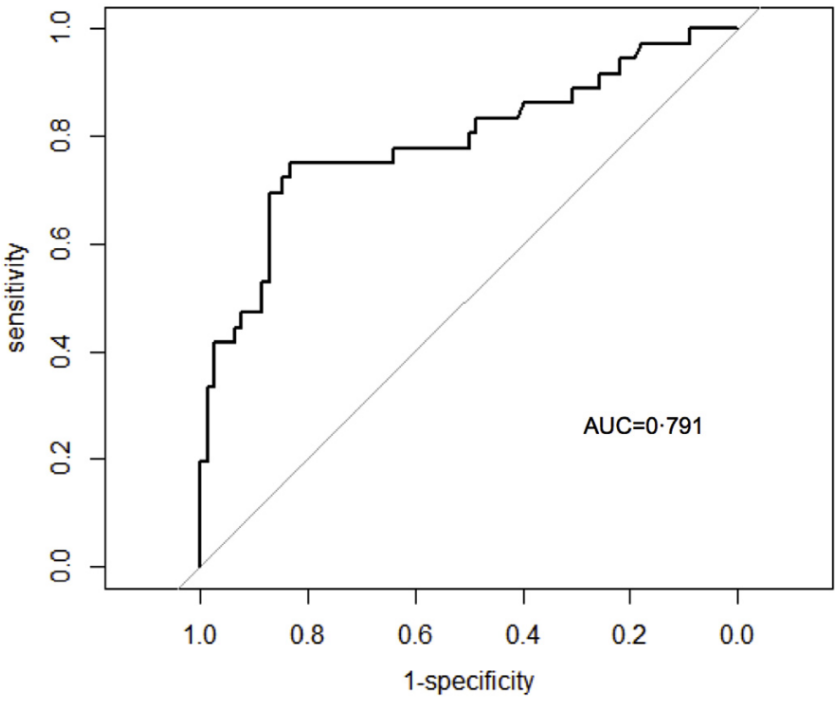
sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
AUC=0·791
1.0
0.8
0.6
0.4
0.2
0.0
1-specificity

FIGURE LEGEND

Figure 1. Ambulatory blood pressure monitoring in Parkinson disease. Examples of two patients, with normal autonomic function (A) and with dysautonomia (B).

Figure 2. ROC curve. Accuracy of systolic blood pressure day-to-night difference in the diagnosis of dysautonomia (%).

TABLES

Table 1. Demographic and clinical characteristics of the study population

	Total (n=114)	**Dysautonomia (n=36)**	**Normal autonomic function (n=78)**	**p**
Demographic characteristics				
Age [years]	64 ± 10	68 ± 10	63 ± 9	< 0.001
Duration of PD [years]	6 ± 4	8 ± 4	6 ± 3	0.003
Comorbid essential hypertension [%]	30 (26%)	12 (33%)	18 (23%)	0.248
Antihypertensive therapy	33 (29%)	14 (39%)	19 (24%)	0.112
Levodopa LEDD [mg]	470.8 ± 365.0	707.8 ± 399.9	361.4 ± 290.6	< 0.001
Dopamine agonists LEDD [mg]	170.8 ± 141.7	130.8 ± 152.9	189.3 ± 133.2	0.016
Total LEDD [mg]	698.7 ± 366.9	898.4 ± 419.7	606.5 ± 300.5	< 0.001
Bedside blood pressure				
Supine SBP [mmHg]	132 ± 16	137 ± 18	129 ± 14	0.015
Supine DBP [mmHg]	79 ± 9	82 ± 9	78 ± 8	0.033
Orthostatic SBP [mmHg]	117 ± 17	111 ± 22	120 ± 14	0.031
Orthostatic DBP [mmHg]	75 ± 10	72 ± 12	77 ± 9	0.028
Orthostatic hypotension [%]	51 (45%)	25 (69%) neurogenic	26 (33%) non neurogenic	< 0.001
Supine hypertension [%]	35 (31%)	18 (50%)	17 (22%)	0.002

24h-blood pressure monitoring				
day SBP [mmHg]	122 ± 10	120 ± 9	123 ± 10	0.067
day DBP [mmHg]	74 ± 8	72 ± 7	75 ± 8	0.136
day SBP Load [%]	14.9	14.3	15.2	0.658
day DBP Load [%]	10.8	11.4	10.8	0.737
night SBP [mmHg]	117 ± 15	126 ± 17	113 ± 13	< 0.001
night SBP [mmHg]	68 ± 10	73 ± 12	65 ± 8	0.001
night SBP Load [%]	25.0	62.0	14.5	< 0.001
night DBP Load [%]	28.1	49.7	22.4	0.001
DND SBP [%]	4.1	-2.8	8.2	< 0.001
DND DBP [%]	9.1	-0.6	12.3	< 0.001
Blood pressure patterns				
Reverse dippers	37 (32%)	25 (69%)	12 (15%)	< 0.001
Reduced dippers	37 (32%)	5 (14%)	32 (41%)	
Dippers	33 (29%)	6 (17%)	27 (35%)	
Extreme dippers	7 (6%)	0 (0%)	7 (9%)	

day: daytime; DBP: diastolic blood pressure; DND: day-night difference; LEDD: levodopa equivalent daily dose; Load: percentage of blood pressure values higher than normal limits; night: night-time; PD: Parkinson disease; SBP: systolic blood pressure.

p, p-value of the comparison between patients with dysautonomia and normal autonomic function.

Table 2. ROC curves: capacity of blood pressure parameters to diagnose dysautonomia

	AUC	**Cut-off**	**Specificity**	**Sensitivity**	**Accuracy**	**NPV**	**PPV**
DND SBP [%] (CI)	0.791 (0.693-0.890)	2.55	0.83 (0.73-0.91)	0.75 (0.58-0.88)	0.81 (0.72.0.87)	0.88 (0.80-0.93)	0.68 (0.55-0.78)
DND DBP [%](CI)	0.783 (0.677-0.883)	6.37	0.83 (0.73-0.91)	0.72 (0.55-0.86)	0.80 (0.71-0.87)	0.87 (0.79-0.91)	0.67 (0.54-0.77)
night SBP [mmHg] (CI)	0.730 (0.629-0.831)	111.5	0.56 (0.45-0.67)	0.81 (0.64-0.92)	0.64 (0.54-0.73)	0.86 (0.76-0.92)	0.46 (0.39-0.53)
night DBP [mmHg] (CI)	0.692 (0.584-0.801)	68.5	0.71 (0.59-0.80)	0.69 (0.52-0.83)	0.70 (0.61-0.78)	0.83 (0.75-0.89)	0.52 (0.42-0.62)

CI: confidence intervals; AUC: area under the curve; DBP: diastolic blood pressure; DND: day-to-night difference; night: night-time; NPV: negative predictive value; PPV: positive predictive value; SBP: systolic blood pressure.