

Machine learning applied to ambulatory blood pressure monitoring: a new tool to diagnose autonomic failure?

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1 **Machine Learning applied to Ambulatory Blood Pressure Monitoring: A New Tool to Diagnose**
2 **Autonomic Failure?**

3

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ABSTRACT

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Background

Autonomic failure (AF) complicates Parkinson's disease (PD) in one-third of cases, resulting in complex blood pressure (BP) abnormalities. While autonomic testing represents the diagnostic gold standard for AF, accessibility to this examination remains limited to few tertiary referral centers.

Objective

The present study sought to investigate the accuracy of a machine learning algorithm applied to 24-h ambulatory BP monitoring (ABPM) as a tool to facilitate the diagnosis of AF in patients with PD.

Methods

Consecutive PD patients naïve to vasoactive medications underwent 24h-ABPM and autonomic testing. The diagnostic accuracy of a Linear Discriminant Analysis (LDA) model exploiting ABPM parameters was compared to autonomic testing (as per a modified version of the Composite Autonomic Symptom Score not including the sudomotor score) in the diagnosis of AF.

Results

The study population consisted of n= 80 PD patients (33% female) with a mean age of 64±10 years old and disease duration of 6.2±4 years. The prevalence of AF at the autonomic testing was 36%. The LDA model showed 91.3% accuracy (98.0% specificity, 79.3% sensitivity) in predicting AF, significantly higher than any of the ABPM variables considered individually (hypotensive episodes= 82%; reverse dipping= 79%; awakening hypotension= 74%).

Conclusion

LDA model based on 24-h ABPM parameters can effectively predict AF, allowing greater accessibility to an accurate and easy to administer test for AF. Potential applications range from systematic AF screening to monitoring and treating blood pressure dysregulation caused by PD and other neurodegenerative disorders.

54 **INTRODUCTION**

55 Autonomic failure (AF) complicates Parkinson’s disease (PD) in up to one-third of cases. Cardiovascular AF disrupts
56 neural networks controlling blood pressure (BP) and heart rate (HR), resulting in complex abnormalities in BP control,
57 such as orthostatic hypotension (OH), supine hypertension (SH), abnormal circadian rhythm, and increased BP
58 variability (BPV) [1]. These abnormalities are usually asymptomatic and difficult to recognize by clinical assessment
59 alone [2][3]. Still, they may result in organ damage [4] and functional disability [5], leading to greater morbidity and
60 quality of life impairment [6], as well as worse clinical prognosis [7].

61
62 Unfortunately, accessibility to cardiovascular autonomic reflex testing (CART), the gold standard for diagnosing AF, is
63 limited due to the complexity of the examination, technical skillset, and expensive equipment required to carry out this
64 complex diagnostic test [8]. As a result, only patients complaining of “classic” OH symptoms, such as postural light-
65 headedness or fainting, are usually referred to CART, and the execution of the test may require long travels to highly
66 specialized tertiary referral centers.

67
68 Recent studies showed that selected abnormalities in the 24-hour BP profiles, such as a reversed circadian rhythm [9]
69 and increased BPV [10], are associated with AF. The central hypothesis of the present study is that ABPM effectively
70 predicts adrenergic AF in patients with PD. To test this hypothesis, a prospective non-interventional study was designed
71 to evaluate the diagnostic accuracy of a machine-learning algorithm of ABPM recordings compared to standard
72 adrenergic autonomic testing in a cohort of consecutive PD patients.

73
74 **METHODS**

75 Consecutive patients referred to the Autonomic Unit of the Department of Medical Science, University of Torino (Italy)
76 between September 2016 and June 2019 were offered to participate in a single-centre, cross-sectional study
77 investigating the diagnostic potential of a machine-learning algorithm applied to ABPM as a tool to diagnose AF in PD.

78
79 **Inclusion criteria**

80 Diagnosis of PD as per the EFNS/MDS-ES recommendations [11] for at least 2 years; stable dosage of dopaminergic
81 drugs for at least 4 weeks.

82
83 **Exclusion criteria**

84 Other neurological diseases associated with primary AF (multi-systemic atrophy, pure autonomic failure); diabetes
85 mellitus or diseases potentially associated with secondary AF [12]; non-sinus rhythm or pacemaker-guided cardiac
86 activity; severe cognitive impairment, defined as Montreal Cognitive Assessment (MoCA) score < 21 [13], or any
87 physical impairment preventing the execution and interpretation of CART; medical history of severe impaired renal
88 function, heart diseases, or obstructive sleep apnoea syndrome; and ongoing vasoactive therapy (anti-hypotensive
89 and/or anti-hypertensive) for orthostatic hypotension and/or supine hypertension.

90

91 **Study protocol**

92 After acquisition of written informed consent, those meeting all the inclusion and none of the exclusion criteria
93 underwent CART followed by 24h-ABPM within 10 days.

94

95 ***CART – Technical Execution***

96 Autonomic testing have been performed as per a standard procedure and cardiovagal and adrenergic indexes calculated
97 according to a modified version of the Composite Autonomic Symptom Score (CASS), without the sudomotor score
98 [14]. Briefly, BP and the HR interval were continuously recorded using a beat-to-beat non-invasive monitor (Finometer,
99 Finapres) during the performance of the following standardized tests:

- 100 1) Deep breathing: patients were asked to breathe deeply and evenly at 6 breaths/min for one minute.
- 101 2) Valsalva manoeuvre: patients were asked to blow into a mouthpiece attached to an aneroid pressure gauge at a
102 pressure of 40 mmHg, for 15 seconds.
- 103 3) Head-up tilt test: patients were asked to lie supine on the tilt table for 10 minutes, then the table was tilted up
104 to a 60° upright position for 5 consecutive minutes. For this test, in addition to the beat-to-beat recording, the
105 BP was measured with an automatic sphygmomanometer (Omron, HEM-9219T-E, Japan ©) at baseline, 1
106 min, 3 min, and 5 min

107 BP and HR variations were analysed with a dedicated software (DAN Test Microlab, Padua, Italy) and scored using
108 age-related normal ranges [15].

109

110 ***CART – Data Interpretation***

111 OH was defined as a sustained reduction of systolic blood pressure ≥ 20 mmHg or diastolic blood pressure ≥ 10 mmHg
112 within three minutes from standing [16].

113 SH was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg recorded after at
114 least 5 minutes of supine rest [3].

115 AF was diagnosed when the sum of cardiovagal and adrenergic score was ≥ 2 .

116

117 *ABPM – Technical Execution*

118 24-hour ABPM were performed using a Spacelabs portable device (Spacelabs 90207 - Spacelabs Inc., Redmond, WA,
119 USA ©) with appropriately sized arm-cuff placed on the non-dominant side, as per current guidelines [17]. BP was
120 measured every 15 minutes during both daytime and night-time; patients were asked to record on a diary relevant
121 behavioural and occupational activities, sleep and wake time, and meals.

122

123 *ABPM – Data Interpretation*

124 ABPM was performed according to definitions and reference values for ABPM data interpretation proposed by the
125 European Society of Hypertension [17]. Specifically, the following parameters were derived:

- 126 • BP load, defined as the percentage of blood pressure values exceeding reference values during daytime
127 ($\geq 135/85$ mmHg) and nighttime ($\geq 120/70$ mmHg).
- 128 • Reverse dipping, defined as a systolic day-night difference ≤ 0 mmHg (i.e., average nocturnal systolic BP
129 higher than average diurnal systolic BP).
- 130 • Weighted blood pressure variability (w-BPV), defined as the sum of standard deviation of diurnal and
131 nocturnal systolic BP, normalized for daytime and night-time duration. W-BPV was considered increased
132 when > 11 [18].
- 133 • Postprandial hypotension (PPH), defined as a reduction in systolic blood pressure ≥ 20 mmHg within 120
134 minutes after a meal, using the mean of the last three BP measurements before the meal as reference [19].
- 135 • Hypotensive episodes, defined as any record of systolic BP values lower than average 24-hour systolic BP by
136 at least 15 mmHg between awakening and lunch time (Hypo-ep ^{$\Delta 15/24h$}) [20].
- 137 • Awakening hypotension, defined as the presence of at least one Hypo-ep ^{$\Delta 15/24h$} within 90 minutes from
138 awakening (Hypo-aw ^{$\Delta 15/24h$}) [20].

139

140 **Statistical analysis.**

141 Analyses were performed with SPSS (Statistical Package for the Social Sciences – version 22 - © 2014 IBM). Normal
142 distribution of continuous variables was tested using the Shapiro-Wilk test. Continuous variables were expressed as
143 mean \pm standard deviation. Qualitative variables were expressed as absolute values of frequency and percentage values.
144 Differences between two independent groups were evaluated using Student's t-test for continuous variables with normal
145 distribution and Mann-Whitney test for continuous variables with non-normal distribution; multiple comparisons

146 (between more than 2 groups) were evaluated with One-way ANOVA analysis and Bonferroni's correction. Categorical
147 variables were compared using chi-square test or Fisher's exact test according to sampling number of analysed groups.

148

149 Univariate logistic regression analysis was used to evaluate the correlation between selected categorical ABPM
150 abnormalities and AF; subsequently, multivariate logistic regression was performed to correct for age, sex, LEDD and
151 disease duration. P-values less than 0.05 were considered statistically significant.

152

153 *Diagnostic accuracy of single ABPM parameters*

154 For categorical variables, 2x2 contingency tables were built setting ABPM parameters as diagnostic test and the
155 presence of AF as real outcome. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value
156 (NPV) were then calculated.

157

158 For continuous variables, a receiver operating characteristic (ROC) analysis was used to estimate the predictive
159 accuracy (state variable: presence of autonomic failure; test variable: ABPM continuous parameters). Sensitivity,
160 specificity, PPV, and NPV were calculated after selection of the optimum ROC cut point, based on the balance between
161 sensitivity and specificity (highest Youden index).

162

163 *Global ABPM diagnostic accuracy - Linear discriminant analysis*

164 Supervised machine learning algorithms were trained using Python 3.5 (library, scikit-learn). Linear discriminant
165 analysis (LDA) [21][22] was applied to develop a prediction model for AF in PD based on ABPM data. LDA employs
166 linear combinations of variables to maximize the separation between groups by increasing precision estimates by
167 variance reduction. The algorithm computes a set of coefficients for linear combination of each variable to predict the
168 diagnosis of AF. The estimation is derived from the following equation: AF diagnosis = $LDA_{coeff1} * Variable_1 +$
169 $LDA_{coeff2} * Variable_2 + \dots + LDA_{coeffn} * Variable_n > \text{cut-off}$. The presence/absence of AF was set as an outcome; the
170 following variables were used to train the model: 24-hour, daytime and nighttime blood pressure values (systolic, mean,
171 and diastolic), 24-hour, daytime and nighttime blood pressure standard deviations (SD), daytime and nighttime blood
172 pressure loads (systolic and diastolic), w-BPV, PPH, reverse dipping, Hypo-aw^{Δ15/24h}, number of Hypo-ep^{Δ15/24h}.

173

174 **RESULTS**

175 The study population consisted of 80 PD patients, 54 males (67.5%) and 26 females (32.5%), with a mean age of 64±10
176 years, and PD duration of 6.2±4 years. All patients were treated with dopaminergic drugs with a Levodopa Equivalent
177 Daily Dose (LEDD) of 668±351 mg [23].

178
179 According to the CART assessment, 29 patients (36%) were diagnosed with AF (AF+). This group was older but had
180 similar disease duration and LEDD compared to the group without AF (AF-). Night-time average BP and BP loads were
181 higher in patients AF+. Also, this group showed higher incidence of reverse dipping, increased SD of systolic daytime
182 BP, and hypotensive episodes compared to AF- (Table 1).

183
184 The LDA model was able to discriminate patients AF+ with 91.3% accuracy, 98.0% specificity, and 79.3% sensitivity,
185 which was significantly higher than any of the ABPM variables considered individually [Table 2 and Figure 1]. The
186 algorithm misdiagnosed only 6 patients with AF; among them, 1 with prevalent cardiovagal, 2 with prevalent
187 adrenergic, and 3 with mixed AF.

188
189 Further analyses were performed to determine the association of AF+ with individual variables while taking into
190 consideration confounders, such as age, sex, disease duration and LEDD. Logistic regression analysis showed a strong
191 association of AF+ with Hypo-aw $\Delta^{15/24\text{h}}$, ≥ 3 Hypo-ep $\Delta^{15/24\text{h}}$, and reverse dipping pattern [Table 3], while the
192 association with increased standard deviation of daytime systolic BP was not confirmed at the multivariate analysis.
193 Nocturnal BP was also associated with AF+, with the mean BP value showing the strongest association (OR 1.09, $p <$
194 0,01) [Table 3B].

195 196 **DISCUSSION**

197 In this study, the diagnostic performance of a supervised learning algorithm employing ABPM recordings to diagnose
198 AF in patients with PD was assessed. The model was able to discriminate AF with 91.3% accuracy, much higher than
199 any of the other ABPM variables considered independently. In particular, while individual ABPM parameters, such as
200 ≥ 3 hypotensive episodes, awakening hypotension, reverse dipping, or increased nocturnal BP could identify AF with
201 relatively good specificity, they were all limited by low sensitivity (<60%), hampering their potential as a screening
202 tool.

203
204 Clinical manifestations of AF encompass both short- and long-term dysregulations in BP regulatory mechanisms. The
205 former include OH and SH, the latter include nocturnal hypertension, abnormal circadian rhythm, and increased BPV

206 [1]. SH and reverse dipping, in particular, have been associated with hypertensive end-organ damage and worse clinical
207 prognosis in patients with PD [24][25][4]. Still, the extent to which a correction of these hemodynamic abnormalities
208 might result in clinical benefit remains to be clarified. The introduction of a machine-learning-based algorithm of 24-h
209 ABPM bears the promise to help understand the complex interaction between hemodynamic parameters and functional
210 outcomes. A deeper understanding of BP dysregulation in AF will allow detecting profiles of BP abnormalities with a
211 higher risk of adverse outcomes and inform the selection of treatment priorities (e.g., balancing risk and benefits of
212 better control of SH at the expense of higher burden of OH versus allowing higher supine and nocturnal BP to mitigate
213 OH) [26][27].

214
215 The present analyses confirm the previous finding that hypotensive episodes and reverse dipping are accurate markers
216 of AF in PD [20][9], while increased BPV seems to be less effective in predicting AF, despite the multiple hypotensive
217 episodes (expected to increase BPV) observed in this patient population. While this result partly conflicts with a
218 previous study [10] suggesting that exaggerated SD of diurnal systolic BP could be used to detect primary or secondary
219 AF, the authors did not confirm the association between AF and increased SD-SBP when the PD status and
220 dopaminergic treatment were included in the multivariate analysis. This suggest that AF in PD (and possibly other
221 forms of primary AF) may be characterized by a peculiar BP profile, different from the one observed in secondary AF.

222
223 The strength of this study is the innovative approach involving machine learning for the detection of AF, that
224 demonstrated high accuracy and specificity, and relatively high sensitivity.

225 The assessment of patients in their real-life environment allows exploring the everyday BP profiles, which may be more
226 informative on the risk of organ damage development than the standardized but artificial values obtained through
227 CART. Several limitations, however, should also be considered in the interpretation of the results.

228 First, the number of patients with AF was relatively low due to the stringent exclusion criteria, aiming at limiting
229 confounders related to additional pharmacological treatment or concurrent clinical conditions; in order to reduce this
230 bias, patients were carefully selected without vasoactive medications or known cardiovascular comorbidities, or severe
231 cognitive impairment. Second, dopaminergic drugs have not been withheld during CART and ABPM to assess BP
232 fluctuations in a real-life environment. Still, the impact of dopaminergic drugs may have influenced the BP recordings.
233 To that extent, the finding that LEDD values were not significantly different among groups and most associations
234 remained significant after adequate correction in multivariate analysis seems reassuring. Third, the possibility exists that
235 ABPM could better capture adrenergic impairment, thus limiting the diagnosis of AF with a prominent cardiovagal
236 impairment, although the analysis of the 6 misidentified patients does not seem to confirm this hypothesis. Fourth, the

237 variability in each individual patient's day schedule might have influenced the ABPM recordings, as those with greater
238 motor disability are less likely to engage in strenuous physical activities or prolonged standing.

239

240 This should be considered as a pilot study, but a wide range of future applications for machine learning in the field of
241 ABPM can be easily envisioned. The machine learning approach needs to be tested and validated on larger samples,
242 evaluating the possibility to discriminate patients with prevalent cardiovagal vs. adrenergic vs. mixed autonomic
243 impairment, with associated clinical implications. It seems reasonable to assume that patients with prevalent
244 cardiovagal impairment should display a peculiar BP profile, since adrenergic vasoconstriction is usually preserved
245 while HR variations are minimal or absent. Similarly, one would expect that patients with prevalent adrenergic
246 impairment, with minimal vasoconstrictive function but preserved compensatory shifts in HR, could be differentiated
247 by those with mixed AF. The extent to which machine learning applied to ambulatory recordings of blood pressure and
248 heart rate can assist in detecting distinctive patterns of blood pressure dysregulation with potentially relevant clinical
249 implications remains to be clarified. In the meantime, these data suggest that this technology can be successfully applied
250 to ABPM recordings to diagnose AF when CART is not easily available or difficult to obtain, favoring more
251 appropriate referrals to a second-level CART evaluation, with the main advantage of lowering healthcare costs,
252 improving the appropriateness of referrals, and providing an additional, real-life, measure of circadian blood pressure
253 fluctuations. Additional possible applications include monitoring the efficacy of treatments aiming at correcting OH
254 without resulting in excessive SH.

255

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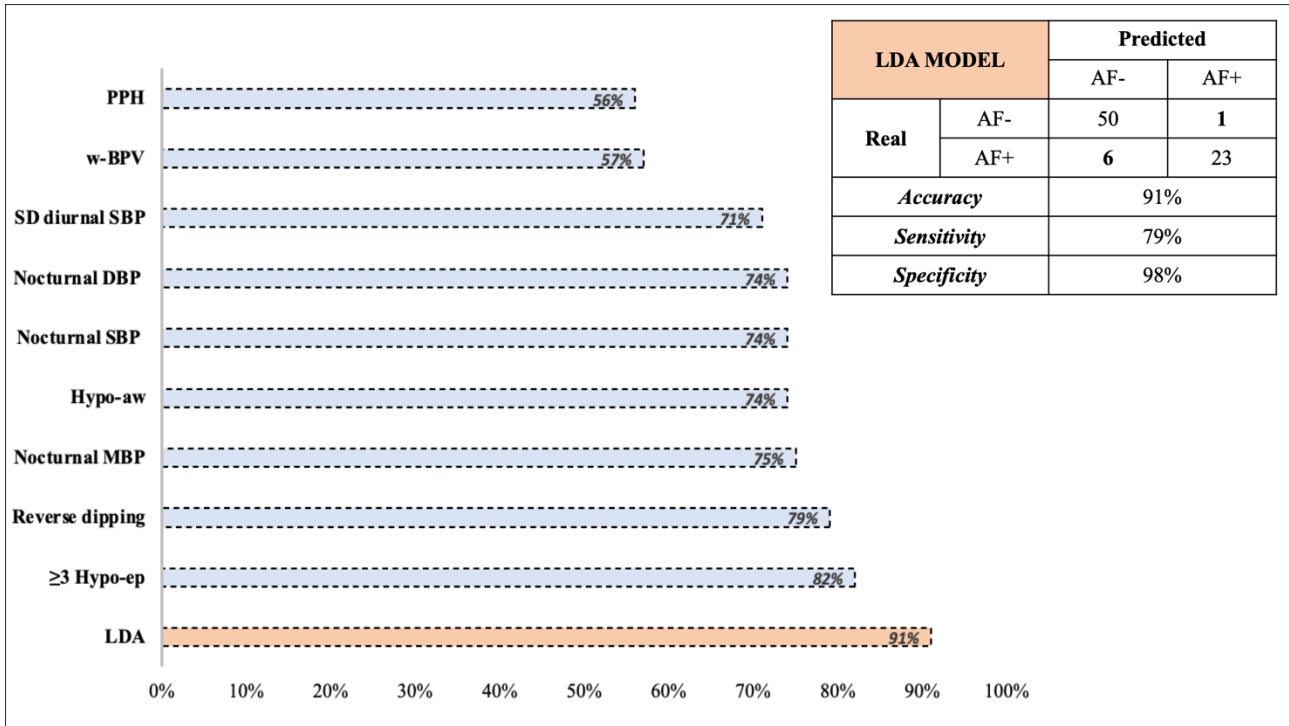
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323

324

325 **FIGURES**

326 **Figure 1. Accuracy of Autonomic Failure prediction**



327

328 *AF: Autonomic failure; PPH: post-prandial hypotension; w-BPV: weighted blood pressure variability; SD: standard*

329 *deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hypo-aw^{A15/24h}: awakening hypotension; MBP:*

330 *mean blood pressure; Hypo-ep^{A15/24h}: hypotensive episodes; LDA: linear discriminant analysis.*

331

332

333 **TABLES**334 **Table 1. ABPM parameters: comparison between patients with and without autonomic failure.**

Ambulatory blood pressure monitoring			
	AF- (n. 51)	AF+ (n. 29)	p-value
Age [years] [mean±SD]	61 ± 10	67 ± 10	< 0.01
Disease duration [years] [mean±SD]	5.5 ± 3	7 ± 4.5	0.08
LEDD [mg] [mean±SD]	657 ± 326	694 ± 403	0.72
Female Sex [n (%)]	17 (33)	9 (31)	0.08
Daytime SBP [mmHg] [mean±SD]	122 ± 10	118 ± 8	0.04
Daytime MBP [mmHg] [mean±SD]	91 ± 9	88 ± 7	0.24
Daytime DBP [mmHg] [mean±SD]	75 ± 9	73 ± 7	0.13
Night-time SBP [mmHg] [mean±SD]	109 ± 11	122 ± 17	< 0.01
Night-time MBP [mmHg] [mean±SD]	79 ± 8	89 ± 14	< 0.01
Night-time DBP [mmHg] [mean±SD]	64 ± 8	71 ± 13	< 0.01
Daytime SBP loads [%] [mean±SD]	19 ± 20	15 ± 11	0.19
Daytime DBP loads [%] [mean±SD]	17 ± 22	18 ± 15	0.83
Night-time SBP loads [%] [mean±SD]	19 ± 24	46 ± 36	< 0.01
Night-time DBP loads [%] [mean±SD]	23 ± 25	45 ± 37	< 0.01
Reverse dipping pattern [n (%)]	5 (10)	17 (58)	< 0.01
w-BPV > 11 mmHg [n (%)]	25 (49)	20 (68)	0.08
SD-daytime SBP >16 mmHg [n (%)]	4 (8)	10 (34)	0.02
PPH [n (%)]	23 (46)	17 (58)	0.27
Hypo-aw ^{Δ15/24h} [n (%)]	4 (8)	13 (44)	< 0.01
Hypo-ep ^{Δ15/24h} [n.] [mean ± SD]	0.4 ± 0.6	3.4 ± 3.3	< 0.01

335

336 *AF: autonomic failure; LEDD: levodopa equivalent daily dose; SBP: systolic blood pressure; MBP: mean blood*
337 *pressure; DBP: diastolic blood pressure; w-BPV: weighted blood pressure variability; SD-daytime SBP: standard*
338 *deviation of diurnal systolic blood pressure; PPH: post-prandial hypotension; Hypo-aw^{Δ15/24h}: Awakening hypotension;*
339 *Hypo-ep^{Δ15/24h}: hypotensive episodes.*

340

341 **Table 2. Prediction of Autonomic Failure through Machine Learning and single ABPM parameters**

Machine learning (all ABPM variables)	Accuracy	AUC	Specificity	Sensitivity	PPV	NPV
LDA	91% (83-96)	/	98% (90-100)	79% (60-92)	96% (77-99)	89% (80-94)
ABPM predictive variables (categorical)	Accuracy	AUC	Specificity	Sensitivity	PPV	NPV
≥ 3 Hypo-ep ^{Δ15/24h}	82% (71 – 90)	/	100% (93 – 100)	52% (33 – 71)	100%	77% (70 – 83)
Reverse dipping	79% (68 – 87)	/	90% (79 – 97)	59% (39 – 76)	77% (58 – 89)	79% (71 – 86)
Hypo-aw ^{Δ15/24h}	74% (63 – 84)	/	92% (80 – 98)	45% (26 – 64)	76% (54 – 90)	74% (67 – 80)
SD d-SBP (>16 mmHg)	71% (60-81)	/	92% (81-98)	35% (18-54)	71% (46-88)	71% (65-77)
w-BPV (>11 mmHg)	57% (46 – 68)	/	51% (37 – 65)	69% (49 – 84)	44% (36 – 54)	74% (61 – 84)
PPH	56% (44 – 67)	/	54% (39 – 68)	59% (39 – 76)	43% (33 – 53)	69% (58 – 79)
ABPM predictive variables (continuous)	Accuracy	AUC	Specificity	Sensitivity	PPV	NPV
* Diurnal SBP	/	0.62 (0.49-0.75)	/	/	/	/
* Diurnal MBP	/	0.55 (0.42-0.69)	/	/	/	/
* Diurnal DBP	/	0.58 (0.46-0.71)	/	/	/	/
Nocturnal SBP (cut-off 123 mmHg)	74% (67 – 80)	0.72 (0.60-0.84)	90% (79 – 97)	45% (26 – 64)	72% (51 – 87)	74% (67 – 80)
Nocturnal MBP (cut-off 95 mmHg)	75% (64 – 84)	0.73 (0.61-0.85)	96% (87 – 99)	38% (21 – 58)	85% (57 – 96)	73% (67 – 78)
Nocturnal DBP (cut-off 75 mmHg)	74% (63 – 83)	0.67 (0.54-0.80)	92% (81 – 98)	41% (24 – 61)	75% (52 – 89)	73% (67 – 79)

342
343 *Autonomic failure (AF+) was used as outcome. The predictive power of each ABPM variable was calculated through a*
344 *2x2 contingency table for dichotomous variables (Hypo-aw^{Δ15/24h}, ≥ 3 Hypo-ep^{Δ15/24h}, postprandial hypotension, reverse*
345 *dipping pattern, high weighted blood pressure variability) and through the ROC curve for continuous variables*
346 *(diurnal and nocturnal blood pressure values). The accuracy of the continuous variables refers to the cut-point of the*
347 *ROC curve with the best sensitivity-specificity compromise (123 mmHg for SBP, 95 mmHg for MBP, 75 mmHg for*
348 *DBP). LDA: linear discriminant analysis; ABPM: ambulatory blood pressure monitoring; Hypo-aw^{Δ15/24h}: awakening*
349 *hypotension; Hypo-ep^{Δ15/24h}: hypotensive episodes; SD d-SBP: standard deviation of diurnal systolic blood pressure; w-*
350 *BPV: weighted blood pressure variability; PPH: post-prandial hypotension; AUC: area under the curve; PPV: positive*
351 *predictive value; NPV: negative predictive value; SBP: systolic blood pressure; MBP: mean blood pressure; DBP:*
352 *diastolic blood pressure. * The ROC-curve output with diurnal BP value was obtained by inverting the outcome (AF-)*
353 *in order to have an AUC greater than 0.5; accuracy metrics have not been reported being not significant.*

354

355 **Table 3. Univariate and multivariate logistic regression analysis**

Table 3A		Outcome	
ABPM predictive Variables (categorical)		Autonomic Failure	
		Univariate analysis (IC 95%)	Multivariate analysis (IC 95%)
Hypo-aw ^{Δ15/24 h}	OR	9.1 (2.6 – 32)	8.7 (2 – 37.4)
	<i>p</i> -value	< 0.01	0.01
≥ 3 Hypo-ep ^{Δ15/24 h}	OR	40.2 (5.8 – 78)	60.7 (12.1 – 108)
	<i>p</i> -value	< 0.01	< 0.01
PPH	OR	1.6 (0.7 – 4.2)	1.4 (0.4 – 4.5)
	<i>p</i> -value	0.28	0.57
Reverse dipping	OR	13 (4 – 42)	16.6 (3.2 – 87)
	<i>p</i> -value	< 0.01	< 0.01
w-BPV (> 11 mmHg)	OR	2.3 (0.9 – 6)	1.4 (0.5 – 4.3)
	<i>p</i> -value	0.09	0.57
DS daytime SBP (>16 mmHg)	OR	6.1 (1.7 – 22.1)	3.8 (0.9 - 16)
	<i>p</i> -value	< 0.01	0.06

Table 3B		Outcome	
ABPM predictive Variables (continuous)		Autonomic Failure	
		Univariate analysis (IC 95%)	Multivariate analysis (IC 95%)
Diurnal SBP	OR	0.95 (0.9 – 1.01)	0.95 (0.89 – 1.01)
	<i>p</i> -value	0.06	0.06
Diurnal MBP	OR	0.96 (0.9 – 1.01)	0.96 (0.89 – 1.03)
	<i>p</i> -value	0.14	0.24
Diurnal DBP	OR	0.97 (0.91 – 1.02)	0.97 (0.91 – 1.04)
	<i>p</i> -value	0.24	0.41
Nocturnal SBP	OR	1.07 (1.03 – 1.11)	1.06 (1.01 – 1.12)
	<i>p</i> -value	< 0.01	0.01
Nocturnal MBP	OR	1.09 (1.04 – 1.15)	1.08 (1.02 – 1.15)
	<i>p</i> -value	< 0.01	0.01
Nocturnal DBP	OR	1.08 (1.03 – 1.14)	1.07 (1.01 – 1.13)
	<i>p</i> -value	< 0.01	0.03

356
357 *Autonomic failure (AF⁺) was used as dependent variable (outcome). In univariate analysis, the independent variables*
358 *were Hypo-aw^{Δ15/24h} (awakening hypotension), ≥ 3 Hypo-ep^{Δ15/24h} (hypotensive episodes), reverse dipping, w-BPV*
359 *(weighted blood pressure variability), DS-daytime SBP (standard deviation of daytime systolic blood pressure), diurnal*
360 *and nocturnal SBP (systolic blood pressure), diurnal and nocturnal MBP (mean blood pressure), diurnal and nocturnal*

361 *DBP (diastolic blood pressure). In multivariate analysis age, sex, disease duration and LEDD (Levodopa Equivalent*
362 *Daily Dose) were used as potential confounding variables.*