

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

*Original*

Machine learning applied to ambulatory blood pressure monitoring: a new tool to diagnose autonomic failure? / Vallelonga, F., Sobrero, G., Merola, A., Valente, M., Giudici, M., Di Stefano, C., Milazzo, V., Burrello, J., Burrello, A., Veglio, F., Romagnolo, A., Maule, S.. - In: JOURNAL OF NEUROLOGY. - ISSN 0340-5354. - 269:7(2022), pp. 3833-3840. [10.1007/s00415-022-11020-2]

*Availability:*

This version is available at: 11583/2978547 since: 2023-05-16T13:55:22Z

*Publisher:*

SPRINGER HEIDELBERG

*Published*

DOI:10.1007/s00415-022-11020-2

*Terms of use:*

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

*Publisher copyright*

(Article begins on next page)

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

3

4 **Authors list:** F. Vallelonga, MD <sup>a\*</sup>; G. Sobrero, MD <sup>a\*</sup>; A. Merola, MD PhD <sup>c</sup>; M. Valente MD <sup>a</sup>; M. Giudici MD <sup>a</sup>; C.  
5 Di Stefano MD <sup>a</sup>; V. Milazzo MD <sup>a</sup>; J. Burrello MD <sup>a</sup>; A. Burrello <sup>d</sup>; F. Veglio MD <sup>a</sup>; A. Romagnolo, MD <sup>bff</sup>; S. Maule  
6 MD <sup>aff</sup>

7 \* FV and GS joint-first authors

8 ff AR and SM joint-last authors

9

10 a. Department of Medical Sciences, Internal Medicine Division, Autonomic Unit and Hypertension Unit,  
11 University of Turin, via Genova 3, 10126, Turin, Italy

12 b. Department of Neuroscience “Rita Levi Montalcini”, University of Turin, via Cherasco 15, 10124, Turin, Italy

13 c. Department of Neurology, Wexner Medical Center, Ohio State University, Columbus, OH, USA

14 d. Department of Electrical, Electronic and Information Engineering "Guglielmo Marconi" (DEI), University of  
15 Bologna, Bologna, Italy.

16

17 **Corresponding author:**

18 Fabrizio Vallelonga, MD

19 Department of Medical Sciences, Internal Medicine Division

20 Autonomic Unit and Hypertension Unit

21 University of Turin, Turin, Italy.

22 e-mail: vallelonga.fabrizio@gmail.com

23 telephone: +39 011 633 6959 - fax: +39 011 633 6931

24 ORCID iD 0000-0002-4628-6767

25

26 **Word count:** 2402 (excluding abstract and keywords, figures, tables, captions and references).

27

28 **Key words:** supervised learning, linear discriminant analysis, autonomic failure prediction

29

## ABSTRACT

30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

### **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  $\geq 20$  mmHg or diastolic blood pressure  $\geq 10$  mmHg  
112 within three minutes from standing [16].

113 SH was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  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  $\geq 2$ .

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  $\leq 0$  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  $\geq 20$  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 <sup>$\Delta 15/24h$</sup> ) [20].

137 • Awakening hypotension, defined as the presence of at least one Hypo-ep <sup>$\Delta 15/24h$</sup>  within 90 minutes from  
138 awakening (Hypo-aw <sup>$\Delta 15/24h$</sup> ) [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:  $AF \text{ diagnosis} = LDA_{coeff1} * Variable_1 +$   
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<sup>Δ15/24h</sup>, number of Hypo-ep<sup>Δ15/24h</sup>.

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  $\Delta^{15/24\text{h}}$ ,  $\geq 3$  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  $\geq 3$  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

## 256 **BIBLIOGRAPHY**

- 257 1. Vallelonga F, Di Stefano C, Merola A, et al (2019) Blood pressure circadian rhythm alterations in alpha-  
258 synucleinopathies. *J Neurol* 266:1141–1152. <https://doi.org/10.1007/s00415-019-09244-w>
- 259 2. Palma J-A, Gomez-Esteban JC, Norcliffe-Kaufmann L, et al (2015) Orthostatic hypotension in Parkinson  
260 disease: how much you fall or how low you go? *Mov Disord* 30:639–645. <https://doi.org/10.1002/mds.26079>
- 261 3. Fanciulli A, Jordan J, Biaggioni I, et al (2018) Consensus statement on the definition of neurogenic supine  
262 hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European  
263 Federation of Autonomic Societies (EFAS): Endorsed by the European Academy of Neurology (E. Clin Auton  
264 Res 28:355–362. <https://doi.org/10.1007/s10286-018-0529-8>
- 265 4. Palma JA, Redel-Traub G, Porciuncula A, et al (2020) The impact of supine hypertension on target organ  
266 damage and survival in patients with synucleinopathies and neurogenic orthostatic hypotension. *Park Relat*  
267 *Disord* 75:97–104. <https://doi.org/10.1016/j.parkreldis.2020.04.011>

- 268 5. Merola A, Romagnolo A, Rosso M, et al (2018) Autonomic dysfunction in Parkinson's disease: A prospective  
269 cohort study. *Mov Disord* 33:391–397. <https://doi.org/10.1002/mds.27268>
- 270 6. Merola A, Romagnolo A, Rosso M, et al (2016) Orthostatic hypotension in Parkinson's disease: Does it matter  
271 if asymptomatic? *Parkinsonism Relat Disord* 33:65–71. <https://doi.org/10.1016/j.parkreldis.2016.09.013>
- 272 7. De Pablo-Fernandez E, Tur C, Revesz T, et al (2017) Association of autonomic dysfunction with disease  
273 progression and survival in Parkinson disease. *JAMA Neurol* 74:970–976.  
274 <https://doi.org/10.1001/jamaneurol.2017.1125>
- 275 8. (2017) Proper performance of autonomic function testing. *Muscle Nerve* 55:3–4.  
276 <https://doi.org/10.1002/mus.25446>
- 277 9. Milazzo V, Di Stefano C, Vallelonga F, et al (2018) Reverse blood pressure dipping as marker of dysautonomia  
278 in Parkinson disease. *Park Relat Disord* 56:82–87. <https://doi.org/10.1016/j.parkreldis.2018.06.032>
- 279 10. Lodhi HA, Peri-Okonny PA, Schesing K, et al (2019) Lodhi 2019 Usefulness of BP Variability Indices Derived  
280 From 24-Hour ABPM in Detecting Autonomic Failure.pdf. *JAm Hear Assoc*
- 281 11. Berardelli A, Wenning GK, Antonini A, et al (2013) EFNS/MDS-ES recommendations for the diagnosis of  
282 Parkinson's disease. *Eur J Neurol* 20:16–34. <https://doi.org/10.1111/ene.12022>
- 283 12. Dineen J, Freeman R (2015) Autonomic Neuropathy. *Semin Neurol* 35:458–468. [https://doi.org/10.1055/s-](https://doi.org/10.1055/s-0035-1558983)  
284 [0035-1558983](https://doi.org/10.1055/s-0035-1558983)
- 285 13. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al (2010) The MoCA: well-suited screen for cognitive  
286 impairment in Parkinson disease. *Neurology* 75:1717–1725. <https://doi.org/10.1212/WNL.0b013e3181fc29c9>
- 287 14. Low PA (1993) Composite Autonomic Scoring Scale for Laboratory Quantification of Generalized Autonomic  
288 Failure. *Mayo Clin Proc* 68:748–752. [https://doi.org/10.1016/S0025-6196\(12\)60631-4](https://doi.org/10.1016/S0025-6196(12)60631-4)
- 289 15. Low PA, Denq JC, Opfer-Gehrking TL, et al (1997) Effect of age and gender on sudomotor and cardiovagal  
290 function and blood pressure response to tilt in normal subjects. *Muscle and Nerve* 20:1561–1568.  
291 [https://doi.org/10.1002/\(SICI\)1097-4598\(199712\)20:12<1561::AID-MUS11>3.0.CO;2-3](https://doi.org/10.1002/(SICI)1097-4598(199712)20:12<1561::AID-MUS11>3.0.CO;2-3)
- 292 16. Freeman R, Wieling W, Axelrod FB, et al (2011) Consensus statement on the definition of orthostatic  
293 hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res Off J Clin*  
294 *Auton Res Soc* 21:69–72. <https://doi.org/10.1007/s10286-011-0119-5>
- 295 17. Parati G, Stergiou G, O'Brien E, et al (2014) European society of hypertension practice guidelines for  
296 ambulatory blood pressure monitoring. *J Hypertens* 32:1359–1366.  
297 <https://doi.org/10.1097/HJH.0000000000000221>
- 298 18. Bilo G, Giglio A, Styczkiewicz K, et al (2007) A new method for assessing 24-h blood pressure variability after

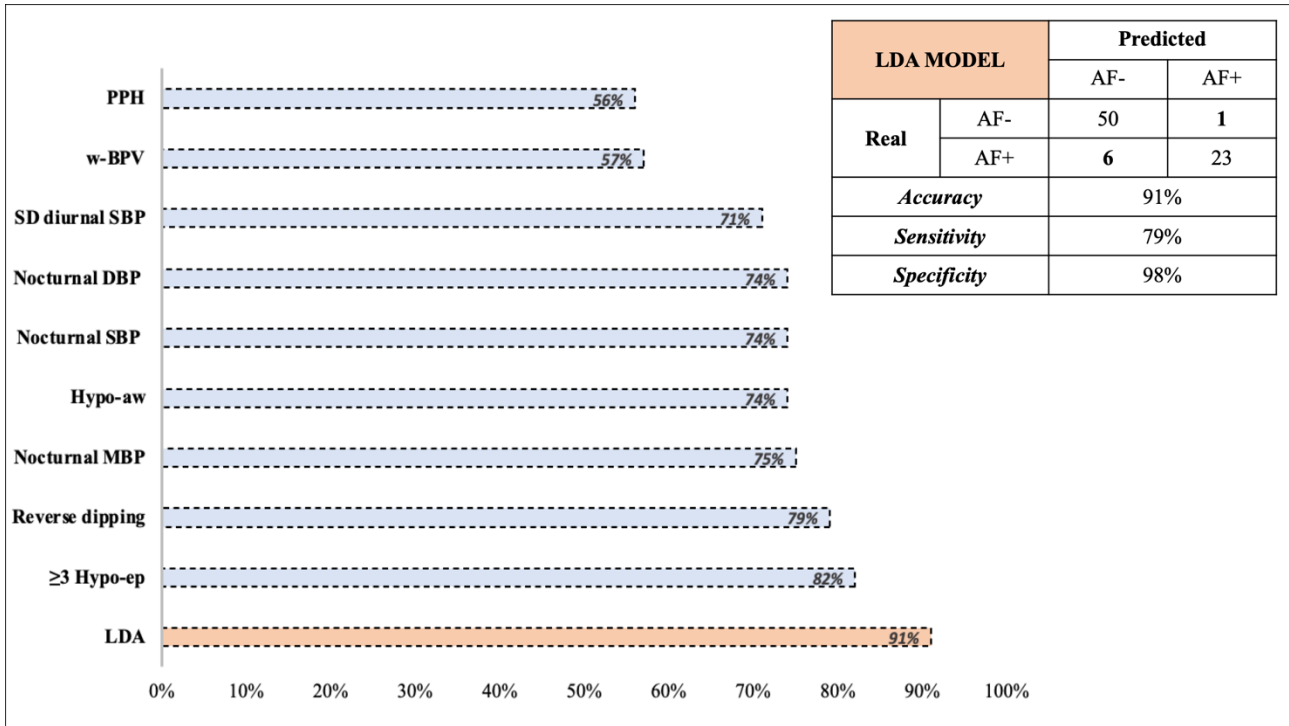
- 299 excluding the contribution of nocturnal blood pressure fall. *J Hypertens* 25:2058–2066.  
300 <https://doi.org/10.1097/HJH.0b013e32829c6a60>
- 301 19. Jansen RW, Lipsitz LA (1995) Postprandial hypotension: epidemiology, pathophysiology, and clinical  
302 management. *Ann Intern Med* 122:286–295. <https://doi.org/10.7326/0003-4819-122-4-199502150-00009>
- 303 20. Vallelonga F, Romagnolo A, Merola A, et al (2019) Detection of orthostatic hypotension with ambulatory  
304 blood pressure monitoring in parkinson’s disease. *Hypertens Res* 42:1552–1560.  
305 <https://doi.org/10.1038/s41440-019-0267-x>
- 306 21. Burrello J, Burrello A, Stowasser M, et al (2020) The Primary Aldosteronism Surgical Outcome Score for the  
307 Prediction of Clinical Outcomes After Adrenalectomy for Unilateral Primary Aldosteronism. *Ann Surg*  
308 272:1125–1132. <https://doi.org/10.1097/SLA.0000000000003200>
- 309 22. Meyer LS, Wang X, Sušnik E, et al (2018) Immunohistopathology and Steroid Profiles Associated With  
310 Biochemical Outcomes After Adrenalectomy for Unilateral Primary Aldosteronism. *Hypertens (Dallas, Tex*  
311 *1979)* 72:650–657. <https://doi.org/10.1161/HYPERTENSIONAHA.118.11465>
- 312 23. Tomlinson CL, Stowe R, Patel S, et al (2010) Systematic review of levodopa dose equivalency reporting in  
313 Parkinson’s disease. *Mov Disord* 25:2649–2653. <https://doi.org/10.1002/mds.23429>
- 314 24. Di Stefano C, Sobrero G, Milazzo V, et al (2020) Cardiac organ damage in patients with Parkinson’s disease  
315 and reverse dipping. *J Hypertens* 38:289–294. <https://doi.org/10.1097/HJH.0000000000002249>
- 316 25. Milazzo V, Di Stefano C, Milan A, et al (2015) Cardiovascular complications in patients with autonomic  
317 failure. *Clin Auton Res Off J Clin Auton Res Soc* 25:133–140. <https://doi.org/10.1007/s10286-015-0275-0>
- 318 26. Vallelonga F, Maule S (2019) Diagnostic and therapeutical management of supine hypertension in autonomic  
319 failure: a review of the literature. *J Hypertens* 37:1102–1111. <https://doi.org/10.1097/HJH.0000000000002008>
- 320 27. Espay AJ, LeWitt PA, Hauser RA, et al (2016) Neurogenic orthostatic hypotension and supine hypertension in  
321 Parkinson’s disease and related synucleinopathies: prioritisation of treatment targets. *Lancet Neurol* 15:954–  
322 966. [https://doi.org/10.1016/S1474-4422\(16\)30079-5](https://doi.org/10.1016/S1474-4422(16)30079-5)

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<sup>15/24h</sup>: awakening hypotension; MBP:*  
 330 *mean blood pressure; Hypo-ep<sup>15/24h</sup>: hypotensive episodes; LDA: linear discriminant analysis.*

331

332

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

<b>Ambulatory blood pressure monitoring</b>			
	<b>AF- (n. 51)</b>	<b>AF+ (n. 29)</b>	<b>p-value</b>
Age [years] [mean±SD]	61 ± 10	67 ± 10	< <b>0.01</b>
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	<b>0.04</b>
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	< <b>0.01</b>
Night-time MBP [mmHg] [mean±SD]	79 ± 8	89 ± 14	< <b>0.01</b>
Night-time DBP [mmHg] [mean±SD]	64 ± 8	71 ± 13	< <b>0.01</b>
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	< <b>0.01</b>
Night-time DBP loads [%] [mean±SD]	23 ± 25	45 ± 37	< <b>0.01</b>
Reverse dipping pattern [n (%)]	5 (10)	17 (58)	< <b>0.01</b>
w-BPV > 11 mmHg [n (%)]	25 (49)	20 (68)	0.08
SD-daytime SBP >16 mmHg [n (%)]	4 (8)	10 (34)	<b>0.02</b>
PPH [n (%)]	23 (46)	17 (58)	0.27
Hypo-aw <sup>Δ15/24h</sup> [n (%)]	4 (8)	13 (44)	< <b>0.01</b>
Hypo-ep <sup>Δ15/24h</sup> [n.] [mean ± SD]	0.4 ± 0.6	3.4 ± 3.3	< <b>0.01</b>

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<sup>Δ15/24h</sup>: Awakening hypotension;*  
339 *Hypo-ep<sup>Δ15/24h</sup>: hypotensive episodes.*

340

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

<b>Machine learning (all ABPM variables)</b>	<b>Accuracy</b>	<b>AUC</b>	<b>Specificity</b>	<b>Sensitivity</b>	<b>PPV</b>	<b>NPV</b>
<b>LDA</b>	91% (83-96)	/	98% (90-100)	79% (60-92)	96% (77-99)	89% (80-94)
<b>ABPM predictive variables (categorical)</b>	<b>Accuracy</b>	<b>AUC</b>	<b>Specificity</b>	<b>Sensitivity</b>	<b>PPV</b>	<b>NPV</b>
$\geq 3$ Hypo-ep <sup><math>\Delta 15/24</math>h</sup>	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 <sup><math>\Delta 15/24</math>h</sup>	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)
<b>ABPM predictive variables (continuous)</b>	<b>Accuracy</b>	<b>AUC</b>	<b>Specificity</b>	<b>Sensitivity</b>	<b>PPV</b>	<b>NPV</b>
* 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 <sup>$\Delta 15/24$ h</sup>,  $\geq 3$  Hypo-ep <sup>$\Delta 15/24$ h</sup>, 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 <sup>$\Delta 15/24$ h</sup>: awakening*  
349 *hypotension; Hypo-ep <sup>$\Delta 15/24$ h</sup>: 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**

<b>Table 3A</b>		<b>Outcome</b>	
<b>ABPM predictive Variables (categorical)</b>		<b>Autonomic Failure</b>	
		<b>Univariate analysis (IC 95%)</b>	<b>Multivariate analysis (IC 95%)</b>
Hypo-aw <sup>Δ15/24 h</sup>	OR	<b>9.1</b> (2.6 – 32)	<b>8.7</b> (2 – 37.4)
	<i>p</i> -value	< 0.01	0.01
≥ 3 Hypo-ep <sup>Δ15/24 h</sup>	OR	<b>40.2</b> (5.8 – 78)	<b>60.7</b> (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	<b>13</b> (4 – 42)	<b>16.6</b> (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	<b>6.1</b> (1.7 – 22.1)	3.8 (0.9 - 16)
	<i>p</i> -value	< 0.01	0.06

<b>Table 3B</b>		<b>Outcome</b>	
<b>ABPM predictive Variables (continuous)</b>		<b>Autonomic Failure</b>	
		<b>Univariate analysis (IC 95%)</b>	<b>Multivariate analysis (IC 95%)</b>
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	<b>1.07</b> (1.03 – 1.11)	<b>1.06</b> (1.01 – 1.12)
	<i>p</i> -value	< 0.01	0.01
Nocturnal MBP	OR	<b>1.09</b> (1.04 – 1.15)	<b>1.08</b> (1.02 – 1.15)
	<i>p</i> -value	< 0.01	0.01
Nocturnal DBP	OR	<b>1.08</b> (1.03 – 1.14)	<b>1.07</b> (1.01 – 1.13)
	<i>p</i> -value	< 0.01	0.03

356  
 357 *Autonomic failure (AF<sup>+</sup>) was used as dependent variable (outcome). In univariate analysis, the independent variables*  
 358 *were Hypo-aw<sup>Δ15/24h</sup> (awakening hypotension), ≥ 3 Hypo-ep<sup>Δ15/24h</sup> (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.*