Usefulness of Blood Pressure Variability Indices Derived From 24-Hour Ambulatory Blood Pressure Monitoring in Detecting Autonomic Failure

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Background—Increased blood pressure (BP) variability and nondipping status seen on 24-hour ambulatory BP monitoring are often observed in autonomic failure (ATF).

Methods and Results—We assessed BP variability and nocturnal BP dipping in 273 patients undergoing ambulatory BP monitoring at Southwestern Medical Center between 2010 and 2017. SD, average real variability, and variation independent of mean were calculated from ambulatory BP monitoring. Patients were divided into a discovery cohort (n=201) and a validation cohort (n=72). ATF was confirmed by formal autonomic function test. In the discovery cohort, 24-hour and nighttime average real variability, SD, and variation independent of mean did not differ significantly between ATF (n=25) and controls (n=176, all P>0.05). However, daytime SD, daytime coefficient of variation, and daytime variation independent of mean of systolic BP (SBP) were all significantly higher in patients with ATF than in controls in both discovery and validation cohorts. Nocturnal BP dipping was more blunted in ATF patients than controls in both cohorts (both P<0.01). Using the threshold of 16 mm Hg, daytime SD SBP yielded a sensitivity of 77% and specificity of 82% in detecting ATF in the validation cohort, whereas nondipping status had a sensitivity of 80% and specificity of 44%. The area under the receiver operator characteristic of daytime SD SBP was greater than the area under the receiver operator characteristic of nocturnal SBP dipping (0.79 [0.66-0.91] versus 0.73 [0.58-0.87], respectively).

Conclusions—Daytime SD of SBP is a better screening tool than nondipping status in detecting autonomic dysfunction. (J Am Heart Assoc. 2019;8:e010161. DOI: 10.1161/JAHA.118.010161.)

Key Words: ambulatory blood pressure monitoring • autonomic function • blood pressure variability • hypertension • labile hypertension • orthostatic hypotension

Patients with autonomic failure (ATF) are known to have marked fluctuation in blood pressure (BP), characterized by hypertension in seated or supine positions and profound orthostatic hypotension.1-3 Identification of ATF is important because these patients are more prone to develop excessive hypotension resulting in syncope and presyncope when treated pharmacologically or nonpharmacologically for hypertension, including treatment with low-salt diet and diuretics.4-6 Although diagnosis of ATF may be confirmed by batteries of autonomic function tests, the number of

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Accompanying Data S1, Tables S1 through S10, and Figures S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010161

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Received June 21, 2018; accepted December 20, 2018.

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Clinical Perspective

What Is New?

- In the patients referred for 24-hour ambulatory blood pressure (BP) monitoring, we found that increased variability of daytime BP, but not nocturnal BP, is associated with autonomic dysfunction.
- Among markers of daytime BP variability, SD of daytime systolic BP showed better diagnostic performance than average real variability, coefficient of variation, variation independent of mean, and residual SD after fast Fourier transformation of systolic and diastolic BP in detecting autonomic failure.
- SD of the daytime ambulatory systolic BP also showed superior diagnostic performance than nondipping status, a common BP phenotype in patients with autonomic failure.

What Are the Clinical Implications?

- SD of the daytime ambulatory systolic BP could be a useful and simple screening tool in patients with suspected autonomic failure, who are prone to have orthostatic hypotension or syncope when treated with usual antihypertensive medications such as diuretics.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

The Institutional Review Board of the University of Texas Southwestern Medical Center approved this study. The requirement for informed consent was waived for this retrospective chart review study. Medical records of all new patients (n=660) referred to the Hypertension Specialty Clinic at the University of Texas Southwestern Medical Center from January 1, 2010 to September 30, 2017 were reviewed. Among these patients, a total of 314 patients underwent 24-hour ABPM for any clinical indications, including suspected autonomic failure, suspected white-coat hypertension, or history of dizziness or unexplained syncope. Patients with persistent arrhythmias, pregnancy, and suboptimal ambulatory BP monitoring with <20 daytime readings or <7 nighttime readings were excluded from the study (n=41), leaving 273 patients for analysis. The overall study design is shown in Figure 1. The full group (n=273) was divided into a discovery cohort (n=201) and a validation cohort (n=72). The discovery cohort consisted of 25 ATF patients and 176 controls, and the validation cohort consisted of 22 ATF patients and 50 controls. Assignment of ATF and control patients to discovery and validation cohorts was performed randomly. In order to ensure that severity of autonomic impairment was matched in both the discovery and validation cohorts, cases were categorized based on adrenergic scores from 1 to 4 (1 with the mildest and 4 with the most severe impairment as described in the Autonomic Function Testing section). Then, cases from each adrenergic score subset were assigned to each cohort in a random manner. This distribution was performed before calculation of BPV indices and without knowledge of BPV results.

Autonomic Function Testing

Tests used to assess autonomic function included the quantitative sudomotor axon reflex test, orthostatic BP and heart rate responses to tilt, heart rate response to deep breathing, the Valsalva ratio, and beat-to-beat BP responses to the Valsalva maneuver, tilt, and deep breathing as previously described. Patients were encouraged to stop all persistent medications such as diuretics.

More recently, newer markers of BP variability (BPV) such as average real variability (ARV), variation independent of mean (VIM), and residual standard deviation (RSD) after fast Fourier transformation have been introduced and proposed to predict cardiovascular events in the general population with or without cardiovascular diseases. Whether any of these new indices of BPV are useful in discriminating patients with ATF from patients who do not have ATF has not been determined.

Therefore, we conducted a study to determine the usefulness of BPV indices derived from ambulatory BP monitoring (ABPM) including SD, coefficient of variation (CV), ARV, VIM, and RSD in detecting ATF. We also compared predictive values of these indices with abnormal nocturnal dipping in detecting autonomic failure.

The data that support the findings of this study are available from the corresponding author on reasonable request.
adrenergic score, which was used to define patients with autonomic failure in our study. Presence of an adrenergic score of at least 1 is required to confirm the diagnosis of autonomic failure in our study. The control group, which comprised 226 patients, included those who were either found to have a normal adrenergic score of 0 (n=15) by AFT or who were not suspected of having autonomic dysfunction and did not undergo AFT (n=211).

**Ambulatory BP Monitoring**

ABPM was conducted using Spacelabs model 90207 or 90227 monitors (Spacelabs, Snoqualmie, WA). Daytime was defined as 0700 to 2159 hours, and nighttime was defined as 2200 to 0659 hours. Measurements were obtained every 20 minutes during the day and every 30 minutes at night. To be consistent with guidelines, only patients with at least 20 daytime readings and 7 nighttime readings were included in the analysis. Nocturnal dipping was calculated using average daytime and nighttime systolic BP (SBP) readings of each patient on 24-hour ABPM. Nondipping status included both blunted nocturnal dipping (defined as <10% reduction in mean nighttime BP compared with mean daytime BP) and reverse dipping (defined as higher mean nighttime BP compared with mean daytime BP).

**Study Variables**

For all patients included in the study, variables were collected using the electronic medical record. These variables included age, sex, ethnicity, body mass index, history of diabetes mellitus, history of stroke, history of cardiovascular disease (including coronary artery disease or carotid disease), history of smoking, history of alcohol use, history of arrhythmias, history of obstructive sleep apnea, history of neurological conditions predisposing to ATF, antihypertensive medications, Parkinson medication, cholesterol levels, serum creatinine, estimated glomerular filtration rate, and clinic BP. All continuous variables are represented in mean±SD. All categorical variables are expressed in numbers (n) and percentage (%). Nocturnal BP dipping and all indices of BPV, including SD, VIM, ARV, CV, and residual SD after fast Fourier transformation, were calculated from 24-hour ABPM for both cohorts (Data S1).

**Statistical Analyses**

Categorical variables in both discovery and validation cohorts were compared using the Fisher exact test, and continuous variables were compared using unpaired t test. All P-values were 2-tailed and were not adjusted for multiple testing, with 95% confidence intervals used. A P<0.05 was considered statistically significant. To evaluate the predictive value of BP variability for ATF, we developed a series of logistic regression models in the discovery cohort, incorporating different BPV indices in the presence or absence of clinical factors associated with autonomic dysfunction, including age, sex, history of Parkinson disease, smoking, history of cardiovascular diseases, use of BP medications, and dopaminergic agonists. Additional sensitivity analysis was performed in which we incorporated mean 24-hour, daytime and nighttime ambulatory BP in the
models. Subsequently, we assessed the diagnostic performance of nocturnal BP dipping and BPV indices in discriminating the presence of ATF using a receiver operator characteristic curve in the validation cohort. A Bayes factor was used to assess the significance of the difference between areas under receiver operator characteristic (AUROC) curves in the validation cohort. The Bayes factor was calculated on 5000 bootstrap samples, for each of which the scoring metric (area under the curve) was used to evaluate the performances of the competing models. Based on bootstrap samples, the number of times model A outperforms model B is divided by the number of times model B outperforms model A, which forms the Bayes factor. We used an unbiased prior, and a Bayes factor of 3 is considered a significant cutoff. The optimal cutoff point derived from the threshold leading to the maximum summation of sensitivity and specificity was determined, using the Youden Index.

We also carried out several analyses to confirm the validity of the BP variability measurements. First, because AFT was conducted only in a proportion of control subjects, we performed additional analysis to compare daytime SD (SD-day) of SBP of all ATF patients (n=47) versus controls (n=15) who had undergone AFT to confirm their phenotypes. To address reproducibility of BPV indices within the same patients, we assessed intraclass correlation of BPV indices within the same subjects from 2 consecutive days in a subgroup of ATF patients in whom ABPM was conducted for more than 48 hours (n=19 in the discovery cohort; n=13 in the validation cohort). All statistical analyses were performed using R studio software (R Foundation, Vienna, Austria) version 3.4.2.

Results

Baseline Characteristics and Variability of BP Measurements

Baseline characteristics of the discovery cohort are shown in Table 1. Patients with ATF were significantly older, more likely to be male, and had a higher prevalence of smoking, coronary artery disease, carotid disease, and Parkinson disease than controls. There was no significant difference in the prevalence of diabetes mellitus, history of stroke, or elevated serum creatinine between the 2 groups. ATF patients were more likely to use dopaminergic agonists, less likely to use diuretics, but more likely to use β-blockers than the control group. The ATF group had higher mean nighttime and 24-hour SBP but lower of diastolic BP than the control group. ATF patients displayed blunted nocturnal BP dipping and had higher prevalence of reverse nocturnal dipping than the control group. As expected, ATF patients had higher composite autonomic scoring scale scores, adrenergic scores, and pressure recovery time, but

| Variables                  | Discovery Cohort | Controls (n=176) | P Value |
|---------------------------|------------------|------------------|---------|
| Age                       | 71.4±9.2         | 58.7±16.1        | 0.0002  |
| Male (%)                  | 16 (64%)         | 75 (43%)         | 0.02    |
| Race/ethnicity            |                  |                  |         |
| Whites (%)                | 22 (88%)         | 120 (68%)        | 0.06    |
| Hispanics (%)             | 0 (0%)           | 8 (4%)           | 0.60    |
| BMI, kg/m²                 | 27±5             | 28±6             | 0.40    |
| Diabetes mellitus (%)     | 4 (16%)          | 26 (14%)         | 0.80    |
| Stroke (%)                | 2 (8%)           | 12 (7%)          | 0.70    |
| Tobacco use (%)           | 6 (24%)          | 11 (6.2%)        | 0.009   |
| CAD (%)                   | 6 (24%)          | 15 (8.5%)        | 0.03    |
| Carotid disease (%)       | 5 (20%)          | 2 (1.1%)         | 0.0004  |
| Serum creatinine, mg/dL   | 1.03±0.39        | 1.02±0.53        | 0.92    |

Table 1. Baseline Characteristics of the Discovery Cohort

BMI indicates body mass index; BP, blood pressure; bpm, beats per minute; CAD, coronary artery disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

*Multisystem atrophy, pure autonomic failure, baroreflex failure, Lewy body dementia, idiopathic autonomic neuropathy, neuroleptic-induced parkinsonism, familial dysautonomia, and idiopathic peripheral neuropathy.
a lower heart rate response to deep breathing and Valsalva heart rate ratio than the control group (Table S1).

SD-day, CV-day, and VIM-day in the discovery cohort were significantly higher in the ATF group compared with the control group (Table 2). Residual SD of SBP after Fourier transformation was also significantly higher in the ATF group than the control group. However, ARV-day and all of 24-hour and nighttime BPV indices were not significantly different.
between the cases and the controls of the discovery cohort (Table 2). The differences between SD-day, CV-day, and VIM-day of SBP between cases and controls were still observed after adjustments using a multivariable model including age, sex, history of Parkinson disease, smoking, and history of cardiovascular diseases (coronary artery disease or carotid disease) and blood pressure medications in models 1 and 2. With addition of Parkinson medications in model 3, the trend was maintained, although these differences did not reach significance at the level of 0.05. The RSD of SBP was no longer significant within the discovery cohort after multivariable adjustment (Table 2). Addition of mean ambulatory blood pressure to the above models did not affect the results (Table S2).

Baseline characteristics of subjects in the ATF group and the control group of the validation cohort are shown in Table S3. Similar to the discovery cohort, we found that SD-day, CV-day, and VIM-day were significantly higher in the ATF group than the control group (20±8 versus 13±5, 0.15±0.06 versus 0.10±0.03, and 1.40±0.60 versus 0.93±0.34 mm Hg, all P<0.001; Figure 2 and Table S4). In addition, SD-24, SD-night, ARV-24, ARV-night, ARV-day, CV-24, CV-day, CV-night, VIM-24, VIM-day, and RSD of SBP were significantly higher in the ATF than the control groups in the validation cohort (Table S4).

**Predictive Modeling of ATF Incorporating BP Variability**

The predictions were made in the validation cohort, and the ROC curves were generated for BPV indices of daytime SBP to compare their diagnostic performance with nocturnal BP dipping in predicting ATF. AUROC of SD-day, CV-day, VIM-day, and residual SD were 0.79 (confidence interval 0.66-0.91), 0.77 (0.63-0.89), 0.77 (0.63-0.89), 0.79 (0.65-0.90), respectively, and were superior to AUROC of nocturnal dipping of 0.73 (0.58-0.87) (Figure 3). Based on Bayes factor analysis, we found that the SD-day, CV-day, VIM-day, and RSD of SBP were superior to nocturnal dipping in predicting ATF (Table 3). SD-day was also superior to CV-day and VIM-day but not significantly different from RSD in predicting ATF (Table 3).

Because reverse dipping and nondipping were also more common in patients with ATF, we compared the diagnostic performance of reverse dipping and nondipping with SD-day of SBP. The AUROC of SD-day SBP remains higher than those

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**Figure 2.** Scatter graph showing comparison of SD, coefficient of variation (CV), variation independent of mean (VIM) of SBP in the validation cohort for 24 hour ambulatory SBP, daytime SBP, and nighttime SBP. *P<0.01, †P<0.001. SBP indicates systolic blood pressure.
of reverse nocturnal dipping (Figure S1A) and nondipping (Figure S1B), which further supports the application of SD-day SBP in detecting ATF.

To determine the incremental value of SD-day SBP to clinical risk factors associated with ATF, we calculated the impact of adding SD-day SBP to risk factors on the c-statistic. Clinical risk factors found to be significantly different between ATF and controls in the discovery cohort including age, sex, smoking, history of coronary artery disease or carotid disease and Parkinson disease (Table 1) are incorporated in the model. We found that the addition of SD-day SBP to the prediction model that included clinical risk factors, which were derived from the discovery cohort and applied to generate AUROC in the validation cohort, improved AUROC from 0.67 (0.54-0.78) to 0.72 (0.58-0.84). We also found that the Bayes factor comparing SD-day SBP plus clinical risk factors with clinical risk factors alone to be highly significant at 69.4.

Using the Youden Index,27 we derived optimum cutoffs for each BPV index from the discovery cohort and applied those to calculate sensitivity and specificity in the validation cohort (Table 4). The SD-day threshold SBP of 16 mm Hg (which is identified as the optimal cutoff point) yielded a sensitivity of 77% and specificity of 82% in detecting ATF in the validation cohort. Nondipping status had a sensitivity of 80% and specificity of 44%, whereas reverse dipping had a sensitivity of 50% and a specificity of 90% in the validation cohort. (Table 4).

**Robustness of BP Variability Measurements**

Additional analysis comparing SD-day SBP in a subset of ATF patients (n=47) versus controls (n=15) who had undergone AFT showed the same results as the main analysis. SD-day SBP remained significantly higher in the ATF patients compared with the control group (Figure S2).

**Table 3.** Bayes Factor Comparing Predictive Value of BPV Indices Versus Nocturnal Dipping in the Validation Cohort

| BPV Indices | Bayes Factor Analysis |
|-------------|-----------------------|
| SD-day SBP vs nocturnal dipping | 3 |
| CV-day vs nocturnal dipping | 2 |
| VIM-day vs nocturnal dipping | 2 |
| Residual SD SBP vs nocturnal dipping | 3 |
| SD-day SBP vs CV-day SBP | 17 |
| SD-day SBP vs VIM-day SBP | 7 |
| SD-day SBP vs residual SD SBP | 2 |

BP indicates blood pressure; BPV, BP variability; CV-day, daytime coefficient of variation; SBP, systolic BP; SD-day, SD of daytime SBP; VIM-day, daytime variation independent of mean.
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There are 3 major findings in this study. First, increased daytime variability of SBP, as evidenced by 24-hour ABPM, is independently associated with ATF. Second, SD of daytime SBP is superior to other indices of short-term BP variability, including residual standard variation, average real variability, variation independent of mean, and coefficient of variation in detecting ATF. Third, the diagnostic performance of SD-day SBP is superior to nondipping or reverse dipping in predicting autonomic failure.

Increased variability of BP, characterized by both supine hypertension and orthostatic hypotension, is a hallmark of ATF.28-31 Earlier studies using invasive intra-arterial BP measurement have revealed increased variability of BP, particularly SBP, in a small number of patients with ATF.29,30 Previous epidemiological studies have shown the mean SD-day SBP to be between 13.6 and 14.9 mm Hg in the general population and in patients with essential hypertension,32,33 which is the range observed in the control group of both discovery and validation cohorts in our study. The mean SD-day SBP of our ATF patients was 18 to 20 mm Hg in both discovery and validation cohorts, which is the range reported to be in the fifth quintile of the population in 1 study.33 Although many normotensive and hypertensive individuals without ATF are expected to have SD-day SBP above 16 mm Hg, we believe that the cutoff of 16 mm Hg allows us to identify patients who display more labile BP during the day and in whom additional testing is warranted to confirm the presence of ATF. This is particularly important because ATF patients are at increased risk of syncope and fall when treated with usual antihypertensive medications.

Our study represents the first to demonstrate the superiority of daytime SD of SBP over nighttime or 24-hour SD of either SBP or DBP in predicting ATF when compared with the control group. The results were consistent in both discovery and validation cohorts, which further supports the validity of these findings. This is likely a reflection of variation in BP induced by both orthostatic changes in BP coupled with postprandial hypotension, which is commonly encountered more during the daytime than during nighttime or sleep. Similarly, SD-day of SBP was also found to be superior to ARV, CV, and RSD in detecting ATF. Previous studies have suggested a potential advantage of ARV over SD in capturing short-term BP fluctuation by accounting for the order of blood pressure readings.17 VIM has a potential advantage over SD in terms of assessing BPV that is independent of the mean level of BP,18 whereas RSD allows assessment of SD of BP after removal of both circadian rhythm and postprandial changes.25 Epidemiological studies in populations without autonomic failure have indicated that ARV, VIM, and RSD predict cardiovascular outcomes and subsequent decline in cognitive function, which is independent of mean BP in some18,20 but not all studies.17 Despite potential advantages of these markers over SD in detecting some aspects of BPV, SD-day turned out to be the most useful in detecting ATF. The increased susceptibility of SD to outliers or extreme BP values may render this index more suitable for ATF screening. Because SD is simpler to calculate than ARV, VIM, and RSD, we believe that our study introduces a practical clinical marker that can be readily adopted in the clinical setting.

Table 4. Comparison of Sensitivity, Specificity, Negative Predictive Value, Positive Predictive Value, and Accuracy in the Validation Cohort

| BPV Index          | Cutoff | Sensitivity | Specificity | PPV | NPV | Accuracy |
|--------------------|--------|-------------|-------------|-----|-----|----------|
| Nondipping status, % | <10    | 80          | 44          | 39  | 85  | 55       |
| Reverse nocturnal dipping, % | <0     | 50          | 90          | 69  | 80  | 78       |
| SD-day SBP, mm Hg   | >16    | 77          | 82          | 65  | 89  | 81       |
| CV-day SBP          | >0.11  | 68          | 74          | 54  | 84  | 72       |
| VIM-day SBP, mm Hg  | >1.0   | 73          | 70          | 52  | 85  | 71       |
| Residual SD SBP, mm Hg | >16   | 72          | 80          | 61  | 87  | 78       |

Cutpoints for SD-day, CV-day, VIM-day, and Residual SD, obtained from the Youden Index in the discovery cohort. BP indicates blood pressure; BPV, BP variability; CV-day, coefficient of variation of daytime SBP; NPV, negative predictive value; PPV, positive predictive value; SBP, systolic BP; SD-day, standard deviation of daytime SBP; VIM-day, variation independent of mean.
We did not find the indices of BPV of DBP to be significantly different in the ATF patients compared with controls. The precise mechanism underlying this observation is not known, but our study results are consistent with previous studies using invasive BP measurement over 24 hours.\textsuperscript{29,30} Generally, the magnitude of changes in SBP is greater than changes in DBP during gravitational stress.\textsuperscript{34} A recent study in patients with history of orthostatic intolerance showed that an abnormal fall in SBP by at least 20 mm Hg was observed in 90% of patients during tilt-table testing, whereas only 55% of patients demonstrated a fall in DBP by more than 10 mm Hg.\textsuperscript{34} Furthermore, the use of an oscillometric BP measurement technique during ABPM was likely to have limited precision in detecting smaller variation in DBP in the ATF patients in our study.

Our study is limited by the small number of autonomic failure cases, which primarily reflects the low prevalence of the disease. The retrospective design of our study may be subjected to selection bias. Nevertheless, the study results were replicated in the validation cohort. The lack of a patient diary also limits an accurate assessment of sleep time, wake-up time, and mealtime BP measurements in all patients because many patients forgot to return or fill out their diary at the time of ABPM. However, our study results are pertinent to a real-world situation in which most patients’ diary information is not available and access to a formal autonomic function laboratory is limited.

Despite these limitations, our study results have clinical implications in the detection of autonomic failure. Autonomic function testing is available only in a limited number of tertiary care centers with dedicated laboratories and specially trained clinicians. On the other hand, ABPM is more widely available and endorsed by many organizations\textsuperscript{1–3,35} to ascertain an individual’s usual level of BP outside the clinic setting. Because our population consists of patients in whom ABPM was obtained to determine BP status accurately as a part of routine clinical practice, we believe that the results of our BPV analysis are applicable to most ABPM obtained for a clinical parameter: the evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neuromuscular and Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation. PM R. 2009;1:14–22.

8. Policy Department, American Association of Neuromuscular & Electrodiagnostic Medicine. Proper performance of autonomic function testing. Muscle Nerve. 2017;55:3–4.

9. Omboni S, Smith AA, van Lieshout JJ, Settels JJ, Langeluysters GJ, Wieling W. Mechanisms underlying the impairment in orthostatic tolerance after nocturnal recumbency in patients with autonomic failure. Clin Sci (Lond). 2001;101:609–618.

10. Mann S, Altman DG, Raftery EB, Bannister R. Circadian variation of blood pressure in autonomic failure. Circulation. 1983;68:477–483.

11. Spallone V, Maiello MR, Morganti R, Mandica S, Frajese G. Usefulness of ambulatory blood pressure monitoring in predicting the presence of autonomic neuropathy in type I diabetic patients. J Hum Hypertens. 2007;21:381–386.

12. Okamoto LE, Gamboa A, Shibao C, Black KB, Diedrich A, Raj SR, Robertson D, Biaggioni I. Nocturnal blood pressure dipping in the hypertension of autonomic failure. Hypertension. 2009;53:363–369.

13. Abdalla M, Caughhey MC, Tanner RM, Booth JN III, Diaz KM, Anstey DE, Sims M, Ravelli J, Mintner P, Viera AJ, Shimbo D. Associations of blood pressure dipping patterns with left ventricular mass and left ventricular hypertrophy in blacks: the Jackson Heart Study. J Am Heart Assoc. 2015;6:e004847. DOI: 10.1161/JAHA.116.004847.

14. McGregor DO, Olsson C, Lynn KL. Autonomic dysfunction and ambulatory blood pressure in renal transplant recipients. Transplantation. 2001;71:1277–1281.

References

1. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation. 2005;111:697–716.

2. O’Brien E, Parati G, Stergiou G, Aamar R, Belin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Luett B, Mailion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Okhuto B, Omboni S, Palatini P, Redon J, Ruiolo LM, Shennan A, Staessen JA, vanMontfrans G, Verdaccia P, Waerber B, Wang J, Zanchetti A, Zhang Y; European Society of Hypertension Working Group on Blood Pressure Monitoring, European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31:1731–1768.

3. JCS Joint Working Group. Guidelines for the clinical use of 24 hour ambulatory blood pressure monitoring (ABPM) (JCS 2010): - digest version. Circ J. 2012;76:508–519.

4. Biaggioni I. The sympathetic nervous system and blood volume regulation: lessons from autonomic failure patients. Am J Med Sci. 2007;334:61–64.

5. Low PA, Tomalia VA. Orthostatic hypotension: mechanisms, causes, management. J Clin Neurol. 2015;11:220–226.

6. Shibao C, Okamoto L, Biaggioni I. Pharmacotherapy of autonomic failure. Pharmacol Ther. 2012;134:279–286.

7. England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, Asbury AK, Szigieth K, Lupsfsi JR, Latov N, Lewis RA, Low PA, Fisher MA, Herrmann D, Howard JP, Lauria G, Miller RG, Polydefkis M, Sumner AJ; American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM R. 2009;1:14–22.

8. Policy Department, American Association of Neuromuscular & Electrodiagnostic Medicine. Proper performance of autonomic function testing. Muscle Nerve. 2017;55:3–4.

9. Omboni S, Smith AA, van Lieshout JJ, Settels JJ, Langeluysters GJ, Wieling W. Mechanisms underlying the impairment in orthostatic tolerance after nocturnal recumbency in patients with autonomic failure. Clin Sci (Lond). 2001;101:609–618.

10. Mann S, Altman DG, Raftery EB, Bannister R. Circadian variation of blood pressure in autonomic failure. Circulation. 1983;68:477–483.

11. Spallone V, Maiello MR, Morganti R, Mandica S, Frajese G. Usefulness of ambulatory blood pressure monitoring in predicting the presence of autonomic neuropathy in type I diabetic patients. J Hum Hypertens. 2007;21:381–386.

12. Okamoto LE, Gamboa A, Shibao C, Black KB, Diedrich A, Raj SR, Robertson D, Biaggioni I. Nocturnal blood pressure dipping in the hypertension of autonomic failure. Hypertension. 2009;53:363–369.

13. Abdalla M, Caughhey MC, Tanner RM, Booth JN III, Diaz KM, Anstey DE, Sims M, Ravelli J, Mintner P, Viera AJ, Shimb D. Associations of blood pressure dipping patterns with left ventricular mass and left ventricular hypertrophy in blacks: the Jackson Heart Study. J Am Heart Assoc. 2015;6:e004847. DOI: 10.1161/JAHA.116.004847.

14. McGregor DO, Olsson C, Lynn KL. Autonomic dysfunction and ambulatory blood pressure in renal transplant recipients. Transplantation. 2001;71:1277–1281.

Acknowledgments

We gratefully acknowledge assistance from Ayodele Agby in data collection and organization.

Sources of Funding

This research was supported by grants from the National Institute of Health (T32-DK007257 NRSA Diversity Supplement Award) to Peri-Okonny, the Lawson & Rogers Lacy Research Fund in Cardiovascular Disease to Mitchell, and National Institute of Health (NIH P30DK079328) to Vongpatanasin (co-director, Clinical and Translational Core). It was also supported by National Institute of Health grants (CCSG 5P30CA142543 and R03 ES026397-01) to Wang.
15. Cuspidi C, Sala C, Tadic M, Gherbesi E, De Giorgi A, Grassi G, Mancia G. Clinical and prognostic significance of a reverse dipping pattern on ambulatory monitoring: an updated review. J Clin Hypertens (Greenwich). 2017;19:713–721.

16. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol. 2013;10:143–155.

17. Hansen TW, Thijis L, Li Y, Boggia J, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Jepsson J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Maleyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Wang J, Ibsen H, O’Brien E, Staessen JA; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. Hypertension. 2010;55:1049–1057.

18. Rothwell PM, Howard SC, Dolan E, O’Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010;375:895–905.

19. Angeli F, Reboldi G, Verdecchia P. Interpretation of ambulatory blood pressure profile: a prognostic approach for clinical practice. J Hypertens. 2015;33:454–457.

20. Manning LS, Rothwell PM, Potter JF, Robinson TG. Prognostic significance of short-term blood pressure variability in acute stroke: systematic review. Stroke. 2015;46:2482–2490.

21. Parati G, Stergiou G, O’Brien E, Aamar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Karlo K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J, Riuilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waebber B, Wang J, Zanchetti A, Zhang Y; European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014;32:1359–1366.

22. Low PA. Autonomic nervous system function. J Clin Neurophysiol. 1993;10:14–27.

23. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc. 1993;68:748–752.

24. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G, Subarans T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005;23:505–511.

25. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Tardivo FO, Grassi G, Sega R. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. Hypertension. 2007;49:1265–1270.

26. Jeffreys H. The Theory of Probability. Oxford, UK: Oxford University Press; 1961.

27. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3:32–35.

28. Tulen JH, Man in ’t Veld AJ, van Steenwijk HG, Mechelse K. Sleep patterns and blood pressure variability in patients with pure autonomic failure. Clin Auton Res. 1991;1:309–315.

29. Mann S, Millar Craig MW, Altman DG, Raftery EB, Hunyor SN. Blood pressure variability in health, hypertension and autonomic failure. Clin Exp Hypertens A. 1985;7:187–194.

30. Mann S, Bellamy GR, Hunyor SN, Raftery EB, Ingall T, Bannister R. Supine hypertension, blood pressure variability and circadian rhythm in autonomic failure: the role of ambulatory intra-arterial monitoring. Clin Exp Pharmacol Physiol. 1984;11:347–350.

31. Alquadan KF, Singhania G, Koratala A, Ejaz AA. Office orthostatic blood pressure measurements and ambulatory blood pressure monitoring in the prediction of autonomic dysfunction. Clin Hypertens. 2017;23:3.

32. Verdecchia P, Borgioni C, Ciucci A, Gattobigio R, Schillaci G, Sacchi N, Santucci A, Santucci C, Reboldi G, Perrellato C. Prognostic significance of blood pressure variability in essential hypertension. Blood Press Monit. 1996;1:3–11.

33. Kikuya M, Hozawa A, Ohkubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Sato H, Ito S, Hisamichi I, Imai Y. Prognostic significance of blood pressure and heart rate variabilities: the Ohasama study. Hypertension. 2000;36:901–906.

34. Fedorowski A, Hamrefors V, Sutton R, van Dijk JG, Freeman R, Lenders JW, Wieking W. Do we need to evaluate diastolic blood pressure in patients with suspected orthostatic hypotension? Clin Auton Res. 2017;27:167–173.

35. Siu AL; US Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:778–786.
Data S1

Supplemental Methods

Indices of Blood Pressure Variability

Standard deviation (SD)

Standard deviation is calculated using the following formula.

$$SD = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n-1}}$$

Residual standard deviation (RSD)

RSD is SD of BP after removal of these recurring cyclic variability components, which is obtained after Fast Fourier transformation (FFT) to remove diurnal BP variation (red line) and post-prandial BP variation (blue line) as shown in the figure below. It is calculated as the mean square of residual BP measurements at each time point after removal of the population-level patterns.

$$RSD = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \hat{x}_i)^2}{n-2}}$$

\(\hat{x}_1, \hat{x}_2, ..., \hat{x}_n\) are fitted values of shared patterns of the whole population derived from FFT.
**Figure:** Black Line: Difference of BP at specific time point from the overall group mean of all patients. Redline: Diurnal group variability pattern for all patients. Blue line: Postprandial BP variation for whole group. Orange line: combined cyclic variation which represents combined effect of both red and blue lines. SD obtained after removal of orange line from each patient’s BP measurements across a whole day would represent residual SD.

**Average real variability (ARV)**

Average real variability (ARV), represents average absolute difference between consecutive measurements. It is thought to be less effected by relatively low frequency of readings recorded in non-invasive monitoring. It has been proposed by some to have superior prognostic value as compared to SD$^3$.

\[
ARV = \frac{1}{n-1} \sum_{i=1}^{n-1} |x_{i+1} - x_i|
\]

**Variation independent of mean (VIM)**

Blood pressure variability is often positively correlated with mean blood pressure level. A measure of variability which is independent of mean level could be a useful tool. VIM is one such index which is derived from SD and is defined as not to correlate with the mean BP levels$^{4-6}$. It is calculated using a fitting curve through a
plot of SD (y-axis) against mean BP (x-axis), for all individuals in the cohort. To be more specific, the regression is performed as $\ln(\text{SD}) = j + p \ln(\text{mean } X)$, and the parameters "j" and "p" are estimated from this regression analysis. With the estimated parameters, VIM is calculated as:

$$VIM = \frac{SD}{j \times x^p}$$
Table S1. Composite Autonomic Scoring Scale (CASS) test results for cases and control within a cohort.

| Variables                        | Discovery Cohort                | Validation Cohort               |
|----------------------------------|---------------------------------|---------------------------------|
|                                  | Cases (n=25) | Controls (n=7) | P-Value | Cases (n=22) | Controls (n=8) | P-Value |
| Adrenergic Score                 | 2.8±1.2       | 0                | -       | 2.6±1.27     | 0                | -       |
| CASS Score                       | 5.04±2.33     | 1.12±1.12        | 0.0002  | 5.36±2.63    | 0.125±0.35       | 0.0001  |
| HRDB Range (nl 7-27 bpm)         | 5.5±5.2       | 11.4±3.3         | 0.008   | 5.8±5.8      | 14±3.2           | 0.0008  |
| E/I Ratio (nl >1.09)             | 1.17±0.1      | 1.19±0.03        | 0.60    | 1.11±0.13    | 1.22±0.10        | 0.03    |
| Valsalva HR Ratio (nl>1.40)      | 1.23±0.16     | 1.67±0.52        | 0.0007  | 1.19±0.19    | 1.67±0.30        | 0.0001  |
| Valsalva BP changes              |                  |                  |         |                |                  |         |
| Δ Early phase 2 - Baseline (mmHg)| 26±18          | 16±11            | 0.17    | 25±16        | 12±7             | 0.03    |
| Δ Late phase 2 – Early phase 2 (mmHg) | 3±4          | 7±5              | 0.03    | 6±9          | 7±3              | 0.76    |
| Δ Phase 4 - Baseline (mmHg)      | -4±8           | 15±20            | 0.0005  | 0.6±16       | 11±13            | 0.11    |
| Valsalva BP Recovery Time (nl < 4 sec) | 20±13       | 2±2              | 0.001   | 16.6±14      | 2.0±1.3          | 0.007   |
| Tilt Table Test                  |                  |                  |         |                |                  |         |
| Supine SBP (mmHg)                | 161±32         | 143±24           | 0.17    | 170±32       | 142±36           | 0.04    |
| Supine DBP (mmHg)                | 76±15          | 77±8             | 0.86    | 86±13        | 72±14            | 0.01    |
| Supine HR (bpm)                  | 65±10          | 69±6             | 0.32    | 65±8         | 71±15            | 0.16    |
| SBP 3 mins post-tilt (mmHg)      | 129±35         | 128±11           | 0.94    | 147±20       | 156±48           | 0.46    |
| DBP 3 mins post-tilt (mmHg)      | 68±15          | 77±8             | 0.14    | 77±14        | 83±27            | 0.42    |
| HR 3 mins post-tilt (bpm)        | 73±18          | 78±10            | 0.48    | 69±9         | 78±17            | 0.06    |
| SBP last reading post-tilt (mmHg)| 135±25         | 122±24           | 0.22    | 139±27       | 137±38           | 0.87    |
| DBP last reading post-tilt (mmHg)| 71±13          | 70±11            | 0.85    | 77±15        | 79±20            | 0.76    |
| HR last reading post tilt (mmHg) | 74±18          | 81±12            | 0.31    | 71±8         | 84±21            | 0.01    |

HRDB = heart rate response to deep breathing
Table S2. Blood Pressure Variability Indices of the Discovery Cohort with addition of mean ambulatory BP to adjustment models.

| BPV Index | Discovery Cohort | P Value | P Value | P Value | P Value |
|-----------|-----------------|---------|---------|---------|---------|
|           | Cases(n=25)     | Controls(n=176) | Unadjusted | Model 1 | Model 2 | Model 3 |
| SD SBP(mmHg) |                  |         |         |         |         |
| SD-24     | 15±7            | 14±5   | 0.28    | 0.33    | 0.56    | 0.69    |
| SD-Day    | 18±8            | 14±5   | 0.01    | 0.01    | 0.05    | 0.08    |
| SD-Night  | 13±6            | 13±5   | 1.00    | 0.39    | 0.40    | 0.31    |
| SD DBP(mmHg) |               |         |         |         |         |
| SD-24     | 10±3            | 9±3    | 0.12    | 0.25    | 0.28    | 0.20    |
| SD-Day    | 10±3            | 11±3   | 0.61    | 0.73    | 0.71    | 0.57    |
| SD-Night  | 8±3             | 9±3    | 0.12    | 0.09    | 0.12    | 0.08    |
| ARV SBP(mmHg) |             |         |         |         |         |
| ARV-24    | 12±3            | 11±3   | 0.13    | 0.55    | 0.81    | 0.74    |
| ARV-Day   | 12±4            | 11±4   | 0.24    | 0.25    | 0.76    | 0.66    |
| ARV-Night | 11±4            | 10±4   | 0.24    | 0.91    | 0.91    | 0.91    |
| ARV DBP(mmHg) |             |         |         |         |         |
| ARV-24    | 7±2             | 7±2    | 1.00    | 0.13    | 0.14    | 0.11    |
| ARV-Day   | 7±2             | 7±2    | 1.00    | 0.62    | 0.51    | 0.47    |
| ARV-Night | 7±3             | 8±2    | 0.11    | 0.06    | 0.09    | 0.07    |
| CV SBP    |                 |         |         |         |         |
| CV-24     | 0.12±0.05       | 0.10±0.03 | 0.20    | 0.46    | 0.70    | 0.78    |
| CV-Day    | **0.13±0.05**   | 0.10±0.04 | 0.01    | 0.02    | 0.06    | 0.09    |
| CV-Night  | 0.10±0.04       | 0.10±0.04 | 1.00    | 0.37    | 0.38    | 0.32    |
| CV DBP    |                 |         |         |         |         |
| CV-24     | 0.12±0.04       | 0.13±0.04 | 0.24    | 0.12    | 0.15    | 0.11    |
| CV-Day    | 0.13±0.04       | 0.12±0.04 | 0.41    | 0.64    | 0.64    | 0.53    |
| CV-Night  | 0.12±0.04       | 0.13±0.04 | 0.23    | 0.23    | 0.25    | 0.22    |
| VIM SBP(mmHg) |               |         |         |         |         |
| VIM-24    | 1.12±0.46       | 1.02±0.35 | 0.20    | 0.46    | 0.70    | 0.78    |
| VIM-Day   | **1.30±0.50**   | 1.02±0.32 | 0.01    | 0.02    | 0.06    | 0.09    |
| VIM-Night | 0.97±0.40       | 1.02±0.40 | 0.55    | 0.30    | 0.31    | 0.27    |
| VIM DBP(mmHg) |               |         |         |         |         |
| VIM-24    | 0.98±0.29       | 1.03±0.30 | 0.43    | 0.20    | 0.23    | 0.17    |
| VIM-Day   | 1.1±0.3         | 1.03±0.33 | 0.53    | 0.70    | 0.69    | 0.55    |
| VIM-Night | 0.93±0.30       | 1.02±0.30 | 0.16    | 0.10    | 0.13    | 0.09    |
| RSD SBP(mmHg) |             |         |         |         |         |
| RSD       | 17±7            | 14±5   | 0.02    | 0.22    | 0.55    | 0.40    |
| RSD DBP(mmHg) |             |         |         |         |         |
| RSD       | 10±3            | 10±3   | 1.00    | 0.56    | 0.43    | 0.34    |
SD=Standard deviation, ARV=Average real variability, CV=Coefficient of variation, VIM=Variation independent of mean, RSD=Residual standard deviation.  24 = 24 hour BP, Day = Daytime BP, Night = Nighttime BP. Model 1= Adjusted for age, sex, smoking, history of coronary artery disease or carotid disease, BP medications (diuretics, alpha agonist or beta blockers) and mean SBP or DBP. Model 2 = Model 1 + Parkinson’s disease, Model 3 = Model 2 + Parkinson’s drugs (carbidopa/levodopa or dopaminergic agonist). Mean BP represents, mean of ambulatory BP corresponding to the timing of BPV markers (e.g., mean 24hr BP for SD-24, mean daytime BP for SD-Day, and mean nighttime BP for SD-night).
Table S3. Baseline Characteristics of the Validation Cohort.

| Variables                        | Validation Cohort |       | P value |
|----------------------------------|-------------------|-------|---------|
|                                  | Cases (n=22)      | Controls (n=50) |       |
| Age                              | 69.7±12.5         | 57.6±17.1 | 0.04   |
| Male (%)                         | 14(64%)           | 25(50%)  | 0.31   |
| **Race/Ethnicity**               |                   |         |        |
| Caucasians (%)                   | 20(91%)           | 28(56%)  | 0.006  |
| Hispanics (%)                    | 1(4%)             | 2(4%)    | 1.00   |
| **BMI (kg/m²)**                  | 25±4              | 28±4    | 0.04   |
| **Diabetes (%)**                 | 4(18%)            | 9(18%)  | 1.00   |
| **Stroke (%)**                   | 0(0%)             | 2(4%)   | 1.00   |
| Tobacco Use (%)                  | 1(4.5%)           | 3(6%)   | 1.00   |
| CAD (%)                          | 1(4.5%)           | 5(10%)  | 0.65   |
| Carotid disease (%)              | 0(0%)             | 2(4%)   | 1.00   |
| Serum Creatinine (mg/dL)         | 1.29±1.05         | 1.01±0.38 | 0.10   |
| **Predisposing Conditions**      |                   |         |        |
| Parkinson's disease              | 8(36.3%)          | 3(6%)   | 0.002  |
| Diabetic Neuropathy              | 2(9.1%)           | 3(6%)   | 0.63   |
| Others*                          | 9(40%)            | 0(0%)   |         |
| Parkinson’s Medications          |                   |         |        |
| Carbidopa/Levodopa               | 5(23%)            | 2(4%)   | 0.02   |
| Dopamine Agonist                 | 5(23%)            | 0(0%)   | 0.001  |
| **BP Medications**               |                   |         |        |
| Diuretics                        | 5(23%)            | 17(34%) | 0.41   |
| Alpha Agonist                    | 2(9.1%)           | 0(0%)   | 0.09   |
| Beta Blockers                    | 3(13.6%)          | 9(18%)  | 0.74   |
| **Office BP (mmHg)**             |                   |         |        |
| Seated SBP                       | 132±33            | 136±21  | 0.53   |
| Seated DBP                       | 77±17             | 78±12   | 0.77   |
| Standing SBP                     | 122±29            | 133±22  | 0.08   |
| Standing DBP                     | 75±17             | 78±14   | 0.43   |
| **Office Pulse (bpm)**           |                   |         |        |
| Sitting                          | 72±9              | 73±17   | 0.79   |
| Standing                         | 78±9              | 80±18   | 0.62   |
| **Ambulatory BP (mmHg)**         |                   |         |        |
| Daytime SBP                      | 140±15            | 130±22  | 0.056  |
| Daytime DBP                      | 79±8              | 74±15   | 0.14   |
| Nighttime SBP                    | 138±23            | 117±21  | 0.0003 |
| Nighttime DBP                    | 76±9              | 64±15   | 0.0009 |
| 24 hours SBP                     | 139±27            | 123±21  | 0.008  |
| 24 hours DBP                     | 77±14             | 69±15   | 0.03   |
| Nocturnal Dipping (%)            | 1.2±1.7           | 9.4±8.2 | 0.001  |
| Non-Dipping (%)                  | 18(82%)           | 28(56%) | 0.06   |
| Reverse Dipping                  | 11(50%)           | 5(10%)  | 0.0004 |

*Multisystem Atrophy, Pure autonomic failure, baroreflex failure, Lewy Body dementia, idiopathic autonomic neuropathy, neuroleptic induced parkinsonism, familial dysautonomia and idiopathic peripheral neuropathy.

BP=Blood pressure, SBP=Systolic blood pressure, DBP=Diastolic blood pressure. Non-dipping= blunted or reverse dipping.
## Table S4. Blood Pressure Variability Indices of the Validation Cohort.

| BPV Index        | Cases (n=22) | Controls (n=50) | P value |
|------------------|--------------|-----------------|---------|
| **SD SBP (mmHg)**|              |                 |         |
| SD-24            | 18±8         | 12±5            | 0.0002  |
| SD-Day           | 20±8         | 13±5            | 0.0001  |
| SD-Night         | 16±7         | 12±5            | 0.007   |
| **SD DBP (mmHg)**|              |                 |         |
| SD-24            | 10±4         | 9±3             | 0.24    |
| SD-Day           | 11±4         | 9±3             | 0.02    |
| SD-Night         | 8±3          | 9±3             | 0.19    |
| **ARV SBP (mmHg)**|             |                 |         |
| ARV-24           | 13±6         | 9±3             | 0.003   |
| ARV-Day          | 15±6         | 9±3             | 0.0001  |
| ARV-Night        | 12±6         | 9±3             | 0.006   |
| **ARV DBP (mmHg)**|             |                 |         |
| ARV-24           | 8±3          | 7±2             | 0.10    |
| ARV-Day          | 9±3          | 7±2             | 0.001   |
| ARV-Night        | 7±2          | 7±2             | 1.00    |
| **CV SBP**       |              |                 |         |
| CV-24            | 0.13±0.05    | 0.10±0.03       | 0.002   |
| CV-Day           | 0.15±0.06    | 0.10±0.03       | 0.0001  |
| CV-Night         | 0.12±0.03    | 0.10±0.03       | 0.01    |
| **CV DBP**       |              |                 |         |
| CV-24            | 0.13±0.04    | 0.13±0.04       | 1.00    |
| CV-Day           | 0.14±0.06    | 0.12±0.04       | 0.10    |
| CV-Night         | 0.11±0.04    | 0.14±0.05       | 0.01    |
| **VIM SBP (mmHg)**|             |                 |         |
| VIM-24           | 1.25±0.50    | 0.96±0.32       | 0.004   |
| VIM-Day          | 1.40±0.60    | 0.93±0.34       | 0.0001  |
| VIM-Night        | 1.10±0.50    | 1.00±0.41       | 0.37    |
| **VIM DBP (mmHg)**|             |                 |         |
| VIM-24           | 1.10±0.30    | 1.00±0.20       | 0.1     |
| VIM-Day          | 1.20±0.40    | 0.98±0.29       | 0.01    |
| VIM-Night        | 0.93±0.36    | 1.00±0.36       | 0.44    |
| **RSD SBP (mmHg)**|             |                 |         |
| RSD-24           | 21±8         | 13±5            | 0.0001  |
| **RSD DBP (mmHg)**|             |                 |         |
| RSD-24           | 11±4         | 9±3             | 0.02    |

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, SD = Standard deviation, ARV = Average real variability, CV = Coefficient of variation, VIM = Variation independent of mean, RSD = Residual standard deviation. -24 = 24 hour BP, -Day = Daytime BP, -Night = Nighttime BP.
Table S5. Comparison of Blood Pressure Variability indices of two consecutive days in patients with confirmed autonomic failure by Pearson’s correlation.

| BPV Index | Discovery Cohort (n=19) | Validation Cohort (n=13) |
|-----------|-------------------------|--------------------------|
|           | Day 1 | Day 2 | CC | Day 1 | Day 2 | CC |
| SD-Day SBP mmHg | 16±6 | 15±6 | 0.87 | 20±10 | 19±9 | 0.95 |
| SD-Day DBP mmHg | 9±3 | 9±3 | 0.72 | 11±5 | 12±5 | 0.96 |
| ARV-Day SBP mmHg | 11±4 | 11±3 | 0.93 | 15±7 | 14±7 | 0.68 |
| ARV-Day DBP mmHg | 7±2 | 7±2 | 0.89 | 10±4 | 9±3 | 0.73 |
| CV-Day SBP | 0.12±0.04 | 0.11±0.04 | 0.81 | 0.14±0.06 | 0.14±0.06 | 0.89 |
| CV-Day DBP | 0.12±0.03 | 0.13±0.04 | 0.74 | 0.14±0.06 | 0.15±0.06 | 0.92 |
| VIM-Day SBP mmHg | 1.18±0.37 | 1.13±0.41 | 0.81 | 1.33±0.60 | 1.35±0.63 | 0.89 |
| VIM-Day DBP mmHg | 1.02±0.27 | 0.99±0.30 | 0.71 | 1.21±0.55 | 1.26±0.53 | 0.94 |

Blood pressure variability (BPV) indices compared between two consecutive days in the discovery and the validation cases. 19 patients in the discovery and 13 patients in the validation cohort had 48 or more hours of ABPM data. No differences in means of BPV were seen between the two days. CC=Pearson’s correlation coefficient
Table S6. Comparison of Blood Pressure Variability indices of two consecutive days in patients with confirmed autonomic failure by intra-class correlation.

| BPV Index  | Discovery Cohort (n=19) | Validation Cohort (n=13) |
|------------|-------------------------|--------------------------|
|            | Day 1 | Day 2 | ICC  | Day 1 | Day 2 | ICC  |
| SD-Day SBP | 16±6  | 15±6  | 0.84 | 20±10 | 19±9  | 0.95 |
| mmHg       |       |       |      |       |       |      |
| SD-Day DBP | 9±3   | 9±3   | 0.72 | 11±5  | 12±5  | 0.95 |
| mmHg       |       |       |      |       |       |      |
| ARV-Day SBP| 11±4  | 11±3  | 0.91 | 15±7  | 14±7  | 0.68 |
| mmHg       |       |       |      |       |       |      |
| ARV-Day DBP| 7±2   | 7±2   | 0.89 | 10±4  | 9±3   | 0.67 |
| mmHg       |       |       |      |       |       |      |
| CV-Day SBP | 0.12±0.04 | 0.11±0.04 | 0.80 | 0.14±0.06 | 0.14±0.06 | 0.90 |
| mmHg       |       |       |      |       |       |      |
| CV-Day DBP | 0.12±0.03 | 0.13±0.04 | 0.74 | 0.14±0.06 | 0.15±0.06 | 0.92 |
| VIM-Day SBP| 1.18±0.37 | 1.13±0.41 | 0.80 | 1.33±0.60 | 1.35±0.63 | 0.90 |
| mmHg       |       |       |      |       |       |      |
| VIM-Day DBP| 1.02±0.27 | 0.99±0.30 | 0.72 | 1.21±0.55 | 1.26±0.53 | 0.95 |

Blood pressure variability (BPV) indices compared between two consecutive days in the discovery and validation cases. 19 patients in the discovery and 13 patients in the validation cohort had 48 or more hours of ABPM data. No differences in means of BPV were seen between the two days. ICC=Intra-class correlation coefficient.
Table S7. Baseline Characteristic of the combined cohort.

| Variables                            | Combined Cohort |        |        |        |
|--------------------------------------|----------------|--------|--------|--------|
|                                      | Cases (n=47)   | Controls (n=226) | P value |
| Age                                  | 71±11          | 58±16  | <0.0001|
| Male (%)                             | 30(64%)        | 100(44%) | 0.02   |
| Race/Ethnicity                       |                |        |        |        |
| Caucasians (%)                       | 42(89%)        | 148(65%) | 0.006  |
| Hispanics (%)                        | 1(2%)          | 10(4%) | 0.70   |
| BMI (kg/m²)                          | 26±4           | 28±5   | 0.01   |
| Diabetes (%)                         | 8(17%)         | 35(15%) | 0.82   |
| Stroke (%)                           | 2(4%)          | 14(6%) | 1.00   |
| Tobacco Use (%)                      | 7(15%)         | 14(6%) | 0.06   |
| CAD (%)                              | 7(15%)         | 20(8%) | 0.30   |
| Carotid disease (%)                  | 5(11%)         | 4(2%)  | 0.009  |
| Serum Creatinine (mg/dL)             | 1.15±0.78      | 1.01±0.45 | 0.09   |
| Predisposing Conditions              |                |        |        |        |
| Parkinson’s disease                  | 17(36%)        | 11(5%) | 0.0001 |
| Diabetic Neuropathy                  | 5(11%)         | 8(3%)  | 0.06   |
| Others*                              | 14(30%)        | 0(0%)  | <0.0001|
| Parkinson’s Medications              |                |        |        |        |
| Carbidopa/Levodopa                   | 13(28%)        | 7(3%)  | <0.0001|
| Dopamine Agonist                     | 10(21%)        | 2(1%)  | <0.0001|
| BP Medications                       |                |        |        |        |
| Diuretics                            | 7(15%)         | 67(30%) | 0.05   |
| Alpha Agonist                        | 7(15%)         | 3(1%)  | 0.0002 |
| Beta Blockers                        | 15(32%)        | 44(19%) | 0.08   |
| Office BP (mmHg)                     |                |        |        |        |
| Seated SBP                           | 135±29         | 138±21 | 0.40   |
| Seated DBP                           | 75±14          | 79±11  | 0.03   |
| Standing SBP                         | 123±27         | 132±24 | 0.02   |
| Standing DBP                         | 72±14          | 78±14  | 0.008  |
| Office Pulse (bpm)                   |                |        |        |        |
| Sitting                               | 71±13          | 73±15  | 0.39   |
| Standing                             | 78±10          | 77±15  | 0.66   |
| Ambulatory BP (mmHg)                 |                |        |        |        |
| Daytime SBP                          | 137±18         | 131±21 | 0.07   |
| Daytime DBP                          | 76±11          | 75±14  | 0.64   |
| Nighttime SBP                        | 135±22         | 119±22 | <0.0001|
| Nighttime DBP                        | 73±11          | 66±14  | 0.001  |
| 24 hours SBP                         | 136±24         | 124±21 | 0.0006 |
| 24 hours DBP                         | 75±14          | 70±14  | 0.03   |
| Nocturnal Dipping (%)                | 0.9±11         | 8±9    | <0.0001|
| Non-Dipping                          | 40(85%)        | 131(58%) | 0.0004 |
| Reverse Dipping                      | 21(45%)        | 41(18%) | 0.0002 |

Multisystem Atrophy, Pure autonomic failure, baroreflex failure, Lewy Body dementia, idiopathic autonomic neuropathy, neuroleptic induced parkinsonism, familial dysautonomia and idiopathic peripheral neuropathy. BP=Blood pressure, SBP=Systolic blood pressure, DBP=Diastolic blood pressure. Non-dipping= blunted dipping or reverse dipping.
Table S8. Composite Autonomic Scoring Scale (CASS) test results for cases and controls in the combined cohort.

| Variables                                  | Combined Cohort | P-Value |
|--------------------------------------------|-----------------|---------|
|                                            | Cases (n=47)    | Controls (n=15) |       |
| Adrenergic Score                           | 2.7±1.2         | 0       | -     |
| CASS Score                                 | 5.20±2.48       | 0.62±0.73 | <0.0001 |
| HRDB Range (nl 7-27 bpm)                   | 5.6±5.5         | 13.0±3.3 | <0.0001 |
| E/I Ratio (nl >1.09)                       | 1.14±0.11       | 1.20±0.06 | 0.04   |
| Valsalva HR Ratio (nl>1.40)                | 1.21±0.17       | 1.43±0.35 | 0.002  |
| Valsalva BP changes                        |                 |         |       |
| Δ Early phase 2 - Baseline (mmHg)          | 26±17           | 20±13   | 0.21   |
| Δ Late phase 2 – Early phase 2 (mmHg)      | 4±6             | 7±4     | 0.07   |
| Δ Phase 4 - Baseline (mmHg)                | -2±12           | 13±16   | 0.0003 |
| Valsalva BP Recovery Time (nl < 4 sec)    | 18±13           | 2.0±1.6 | <0.0001 |
| Tilt Table Test                            |                 |         |       |
| Supine SBP (mmHg)                          | 165±32          | 143±30  | 0.02   |
| Supine DBP (mmHg)                          | 81±14           | 74±11   | 0.08   |
| Supine HR (bpm)                            | 65±9            | 70±9    | 0.06   |
| SBP 3 mins post-tilt (mmHg)                | 138±27          | 142±29  | 0.62   |
| DBP 3 mins post-tilt (mmHg)                | 72±15           | 80±17   | 0.09   |
| HR 3 mins post-tilt (bpm)                  | 71±13           | 78±13   | 0.07   |
| SBP last reading post-tilt (mmHg)          | 137±26          | 128±31  | 0.027  |
| DBP last reading post-tilt (mmHg)          | 74±14           | 74±15   | 1.00   |
| HR last reading post-tilt (mmHg)           | 72±13           | 82±16   | 0.02   |

HRDB = heart rate response to deep breathing
# Table S9. Blood pressure variability indices of the combined cohort.

| BPV Index | Combined Cohort | P Value | P Value | P Value | P Value |
|-----------|-----------------|---------|---------|---------|---------|
|           | Cases(n=47)     | Controls(n=226) | Unadjusted | Model 1 | Model 2 | Model 3 |
| SD SBP(mmHg) |                  |         |         |         |         |
| SD-24     | 17±7            | 13±5    | <0.0001 | 0.0006  | 0.004   | 0.005   |
| SD-Day    | 19±4            | 13±5    | <0.0001 | <0.0001 | 0.0005  | 0.0009  |
| SD-Night  | 15±6            | 13±5    | 0.02    | 0.04    | 0.10    | 0.12    |
| SD DBP(mmHg) |                |         |         |         |         |
| SD-24     | 10±3            | 9±3     | 0.04    | 0.21    | 0.32    | 0.39    |
| SD-Day    | 10±3            | 9±3     | 0.04    | 0.08    | 0.15    | 0.19    |
| SD-Night  | 9±3             | 9±3     | 1.00    | 0.92    | 0.96    | 0.94    |
| ARV SBP(mmHg) |              |         |         |         |         |
| ARV-24    | 12±5            | 10±3    | 0.0003  | 0.004   | 0.01    | 0.01    |
| ARV-Day   | 13±5            | 10±3    | <0.0001 | 0.0008  | 0.005   | 0.003   |
| ARV-Night | 11±5            | 10±4    | 0.14    | 0.05    | 0.10    | 0.10    |
| ARV DBP(mmHg) |              |         |         |         |         |
| ARV-24    | 8±2             | 7±2     | 0.10    | 0.35    | 0.52    | 0.54    |
| ARV-Day   | 8±2             | 7±2     | 0.02    | 0.03    | 0.08    | 0.09    |
| ARV-Night | 7±3             | 8±2     | 0.23    | 0.59    | 0.57    | 0.57    |
| CV SBP    |                  |         |         |         |         |
| CV-24     | 0.12±0.04       | 0.10±0.03 | 0.0001 | 0.004   | 0.02    | 0.03    |
| CV-Day    | 0.14±0.04*      | 0.10±0.03 | <0.0001 | 0.0001  | 0.001   | 0.002   |
| CV-Night  | 0.11±0.04       | 0.10±0.04 | 0.12    | 0.36    | 0.46    | 0.46    |
| CV DBP    |                  |         |         |         |         |
| CV-24     | 0.13±0.04       | 0.13±0.04 | 1.00    | 0.66    | 0.60    | 0.41    |
| CV-Day    | 0.14±0.04       | 0.12±0.04 | 0.12    | 0.27    | 0.44    | 0.63    |
| CV-Night  | 0.12±0.04       | 0.13±0.04 | 0.12    | 0.06    | 0.08    | 0.06    |
| VIM SBP   |                  |         |         |         |         |
| VIM-24    | 1.18±0.48       | 1.01±0.34 | 0.004   | 0.003   | 0.02    | 0.02    |
| VIM-Day   | 1.35±0.50       | 1.00±0.34 | <0.0001 | 0.0002  | 0.001   | 0.003   |
| VIM-Night | 1.00±0.45       | 1.01±0.40 | 0.88    | 0.23    | 0.34    | 0.35    |
| VIM DBP   |                  |         |         |         |         |
| VIM-24    | 1.07±0.35       | 1.02±0.32 | 0.34    | 0.48    | 0.60    | 0.75    |
| VIM-Day   | 1.15±0.40       | 1.01±0.32 | 0.01    | 0.12    | 0.21    | 0.29    |
| VIM-Night | 0.93±0.33       | 1.02±0.32 | 0.17    | 0.55    | 0.57    | 0.48    |
| RSD SBP   |                  |         |         |         |         |
| RSD-24    | 19±7            | 14±5    | <0.0001 | 0.001   | 0.01    | 0.01    |
| RSD       | 10±3            | 10±3    | 1.00    | 0.77    | 0.78    | 0.88    |

SD=Standard deviation, ARV=Average real variability, CV=Coefficient of variation, VIM=Variation independent of mean, RSD=Residual standard deviation. 24 = 24 hour BP,
Day = Daytime BP, Night = Nighttime BP. Model 1 = Adjusted for age, sex, race, BMI and history of carotid disease. Model 2 = Model 1 + Parkinson’s disease, Model 3 = Model 2 + Parkinson’s drugs (carbidopa/levodopa or dopaminergic agonist) and BP medications (diuretics, alpha agonist or beta blockers)
Table S10. Area under the curve (AUROC) for various blood pressure variability indices derived from the combined cohort.

| BPV Index | AUROC |
|-----------|-------|
| **SD SBP(mmHg)** |       |
| SD-24 | 0.71 (0.62-0.79) |
| SD-Day | 0.74 (0.65-0.81) |
| SD-Night | 0.64 (0.56-0.72) |
| **SD DBP(mmHg)** | 0.55 (0.45-0.64) |
| SD-24 | 0.62 (0.53-0.70) |
| SD-Day | 0.64 (0.56-0.72) |
| ARV SBP(mmHg) | 0.66 (0.57-0.75) |
| ARV-24 | 0.70 (0.61-0.77) |
| ARV-Night | 0.61 (0.52-0.70) |
| ARV DBP(mmHg) | 0.51 (0.42-0.61) |
| ARV-24 | 0.61 (0.52-0.70) |
| ARV-Day | 0.61 (0.52-0.70) |
| CV SBP | 0.66 (0.57-0.75) |
| CV-24 | 0.72 (0.64-0.81) |
| CV-Day | 0.56 (0.46-0.65) |
| CV DBP | 0.50 (0.42-0.58) |
| CV-24 | 0.62 (0.52-0.70) |
| CV-Day | 0.61 (0.52-0.69) |
| VIM SBP(mmHg) | 0.67 (0.57-0.76) |
| VIM-24 | 0.72 (0.64-0.80) |
| VIM-Night | 0.57 (0.48-0.66) |
| VIM DBP(mmHg) | 0.53 (0.60-0.77) |
| VIM-24 | 0.62 (0.53-0.71) |
| VIM-Day | 0.56 (0.47-0.66) |
| RSD SBP(mmHg) | 0.64 (0.55-0.73) |
| RSD DBP(mmHg) | 0.54 (0.44-0.63) |
| Nocturnal Dipping | 0.70 (0.60-0.77) |

SD=Standard deviation, ARV=Average real variability, CV=Coefficient of variation, VIM=Variation independent of mean, RSD=Residual standard deviation. 24 = 24 hour BP, Day = Daytime BP, Night = Nighttime BP.
Figure S1a. ROC curve comparing reverse nocturnal dipping with standard deviation of daytime (SD-Day) SBP in detecting underlying autonomic failure.

This reveals superior predictive value of SD-Day, over reverse nocturnal dipping.
Figure S1b. ROC curve comparing non-dipping status with standard deviation of daytime (SD-Day) SBP in detecting underlying autonomic failure.

This reveals superior predictive value of SD-Day, over non-dipping status. SD-Day of SBP
Figure S2. Standard Deviation of daytime (SD-Day) SBP comparison using ambulatory BP monitor data from only those patients, who had completed autonomic function testing, including cases (n=47) and controls (n=15). * P<0.05.
Supplemental References:

1. Imai Y, Aihara A, Ohkubo T, Nagai K, Tsuji I, Minami N, Satoh H and Hisamichi S. Factors that affect blood pressure variability. A community-based study in Ohasama, Japan. *Am J Hypertens*. 1997;10:1281-9.

2. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, Grassi G and Sega R. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension*. 2007;49:1265-70.

3. Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T, Inoue R, Hoshi H, Hashimoto J, Totsune K, Satoh H and Imai Y. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension*. 2008;52:1045-50.

4. Howard SC and Rothwell PM. Reproducibility of measures of visit-to-visit variability in blood pressure after transient ischaemic attack or minor stroke. *Cerebrovasc Dis*. 2009;28:331-40.

5. Rothwell PM, Howard SC, Dolan E, O’Brien E, Dobson JE, Dahlof B, Sever PS and Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895-905.

6. Rothwell PM, Howard SC, Dolan E, O’Brien E, Dobson JE, Dahlof B, Poulter NR, Sever PS, Ascot B and Investigators MRCT. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol*. 2010;9:469-80.