ORIGINAL RESEARCH

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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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.

laboratories dedicated to performing these tests is limited, as they require properly trained personnel and specialized equipment.[7,8] Previous studies using 24-hour ambulatory BP monitoring have demonstrated association between nondipping status and ATF.[9,10] However, the sensitivity of nondipping status in predicting ATF is modest because it has been detected in only 20% to 30% of patients with ATF from diabetic autonomic neuropathy[11] or neurodegenerative disease.[12] Furthermore, nondipping status has also been observed in blacks[13] and with a variety of other conditions not related to ATF, including sleep apnea and chronic kidney disease.[14,15]

More recently, newer markers of BP variability (BPV) such as average real variability (ARV),[16,17] variation independent of mean (VIM),[18,19] and residual standard deviation (RSD)[20] 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.

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[21] 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.[22] Patients were encouraged to stop all antihypertensive drugs for 24 hours before the study. A 10-point composite autonomic scoring scale score is generated during formal autonomic function testing (AFT), as previously described.[22,23] The composite autonomic scoring scale assigns 4 points to the adrenergic component and 3 points each for sudomotor and cardiovagal components. The component most pertinent to autonomic regulation of BP is the

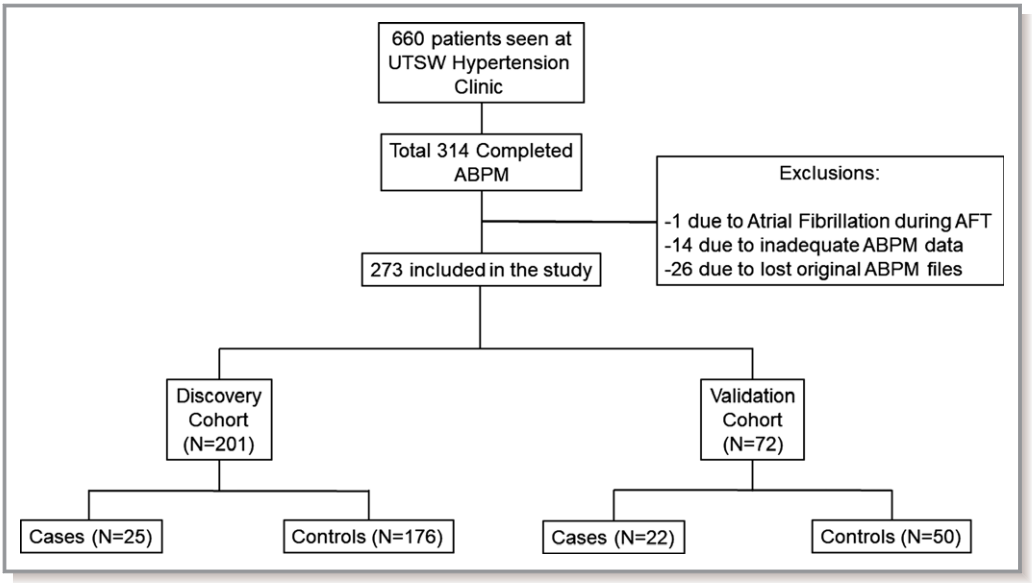

Figure 1. Distribution of the patients in the Discovery and the Validation cohorts. ABPM indicates ambulatory blood pressure monitoring; AFT, autonomic function testing; UTSW, University of Texas Southwestern.

adrenergic score, which was used to define patients with autonomic failure in our study.[22] 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,[21] 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,[18] ARV,[24] CV, and residual SD after fast Fourier transformation,[25] 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[26] 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.[26] The optimal cutoff point derived from the threshold leading to the maximum summation of sensitivity and specificity was determined, using the Youden Index.[27]

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 office seated and standing diastolic BP (DBP) 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

Table 1. Baseline Characteristics of the Discovery Cohort

Variables	Discovery Cohort		*P* Value
	Cases (n=25)	Controls (n=176)	
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/m^2	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
Predisposing conditions			
Parkinson disease	9 (36%)	8 (4.5%)	0.0001
Diabetic neuropathy	3 (12%)	5 (2.8%)	0.06
Others*	5 (20%)	0 (0%)	<0.0001
Parkinson medications			
Carbidopa/levodopa	8 (32%)	5 (2.8%)	0.0001
Dopamine agonist	5 (20%)	2 (1.1%)	0.0004
BP medications			
Diuretics	2 (8%)	50 (28%)	0.02
α-agonists	5 (20%)	3 (1.7%)	0.0009
β-blockers	12 (48%)	38 (21.8%)	0.01
Office BP, mm Hg			
Seated SBP	139±25	141±22	0.72
Seated DBP	73±11	80±11	0.002
Standing SBP	125±26	132±27	0.44
Standing DBP	70±12	79±14	0.006
Office heart rate, bpm			
Sitting	71±18	72±12	0.72
Standing	78±12	75±13	0.32
Ambulatory BP, mm Hg			
Daytime SBP	134±22	131±20	0.44
Daytime DBP	74±14	76±14	0.14
Nighttime SBP	133±21	121±23	0.02
Nighttime DBP	71±13	68±14	0.52
24-hour SBP	134±22	126±22	0.01
24-hour DBP	73±14	72±14	0.06
Nocturnal dipping, %	0.6±10	7±10.3	0.007
Nondipping	22 (88%)	103 (58%)	0.003
Reverse dipping	10 (40%)	36 (20%)	0.04

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

Table 2. Blood Pressure Variability Indices of the Discovery Cohort

	Discovery Cohort		*P* Values			
BPV Index	Cases (n=25)	Controls (n=176)	Unadjusted	Model 1	Model 2	Model 3
SD SBP, mm Hg						
SD-24	15±7	14±5	0.28	0.20	0.33	0.49
SD-day	18±8*	14±5	0.01	0.01	0.04	0.07
SD-night	13±6	13±5	1.00	0.70	0.63	0.47
SD DBP, mm Hg						
SD-24	10±3	9±3	0.12	0.43	0.47	0.36
SD-day	10±3	11±3	0.61	0.97	0.96	0.85
SD-night	8±3	9±3	0.12	0.14	0.18	0.13
ARV SBP, mm Hg						
ARV-24	12±3	11±3	0.13	0.34	0.48	0.52
ARV-day	12±4	11±4	0.24	0.21	0.51	0.51
ARV-night	11±4	10±4	0.24	0.69	0.59	0.66
ARV DBP, mm Hg						
ARV-24	7±2	7±2	1.00	0.30	0.32	0.30
ARV-day	7±2	7±2	1.00	0.88	0.78	0.79
ARV-night	7±3	8±2	0.11	0.13	0.18	0.15
CV SBP						
CV-24	0.12±0.05	0.10±0.03	0.20	0.39	0.60	0.72
CV-day	0.13±0.05*	0.10±0.04	0.01	0.01	0.05	0.08
CV-night	0.10±0.04	0.10±0.04	1.00	0.31	0.32	0.27
CV DBP						
CV-24	0.12±0.04	0.13±0.04	0.24	0.07	0.10	0.07
CV-day	0.13±0.04	0.12±0.04	0.41	0.60	0.60	0.49
CV-night	0.12±0.04	0.13±0.04	0.23	0.10	0.14	0.12
VIM SBP, mm Hg						
VIM-24	1.12±0.46	1.02±0.35	0.20	0.40	0.62	0.73
VIM-day	1.30±0.50*	1.02±0.32	0.01	0.01	0.05	0.08
VIM-night	0.97±0.40	1.02±0.40	0.55	0.30	0.31	0.27
VIM DBP, mm Hg						
VIM-24	0.98±0.29	1.03±0.30	0.43	0.23	0.28	0.28
VIM-day	1.1±0.3	1.03±0.33	0.53	0.83	0.83	0.72
VIM-night	0.93±0.30	1.02±0.30	0.16	0.09	0.12	0.09
RSD SBP, mm Hg	17±7*	14±5	0.02	0.14	0.34	0.29
RSD DBP, mm Hg	10±3	10±3	1.00	0.84	0.68	0.56

Model 1=Adjusted for age, sex, smoking, history of coronary artery disease or carotid disease and BP medications (diuretics, α-agonists, or β-blockers). Model 2=Model 1+Parkinson disease. Model 3=Model 2+Parkinson drugs (carbidopa/levodopa or dopaminergic agonist). 24 indicates 24-hour BP; ARV, average real variability; BP, blood pressure; BPV, BP variability; CV, coefficient of variation; Day, daytime BP; DBP, diastolic BP; Night, nighttime BP; RSD, residual standard deviation; SBP, systolic BP; VIM, variation independent of mean.
*$P < 0.05$.

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), 0S.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

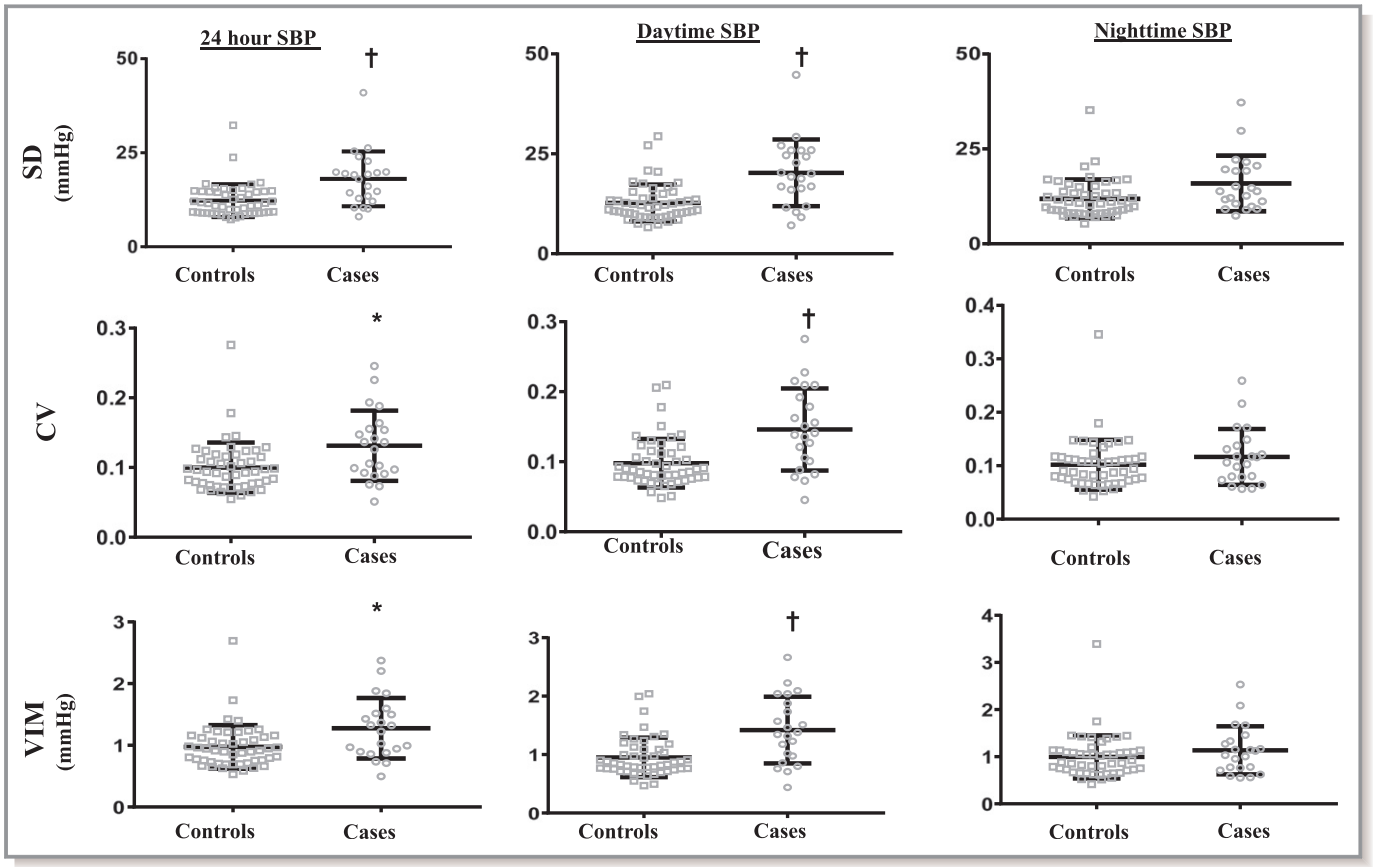

Figure 2. Scatter graph showing comparison of SD, coefficient of variation (CV), variation independent of mean (VIM) of SBP in the validation cohort for 24 hour ambulatory SBP, daytime SBP, and nighttime SBP. *$P<0.01$, †$P<0.001$. SBP indicates systolic blood pressure.

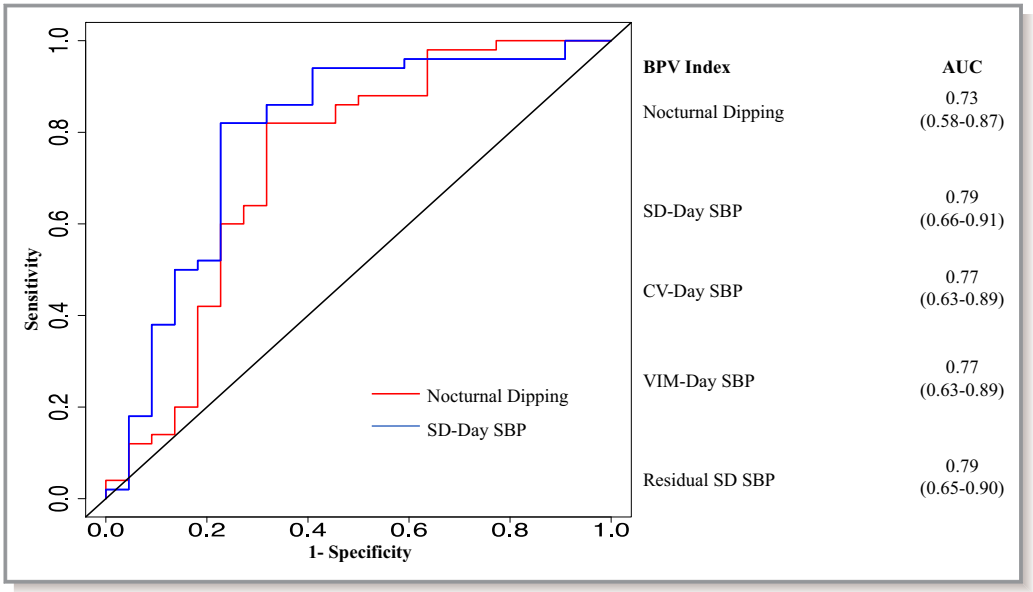

Figure 3. Left: ROC comparing nocturnal dipping with SD of daytime (SD-Day) SBP to detect autonomic failure (ATF). This shows superior predictive value of SD-Day over nocturnal dipping. Right: Comparison of AUCs of various BPV indices of daytime SBP including standard deviation (SD-Day), coefficient of variation (CV-Day), variation independent of mean (VIM-Day) and also Residual SD after Fourier transformation. AUC indicates area under the [receptor operation] curve; BPV, blood pressure variability; SBP, 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+nocturnal dipping vs nocturnal dipping alone	17
SD-day SBP vs CV-day SBP	7
SD-day SBP vs VIM-day SBP	8
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.

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.

To address reproducibility of BPV indices, we compared day-to-day variation 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). We found Pearson and intraclass correlation of the SD-day SBP between 2 consecutive days in the ATF patients to be >80% in both cohorts (Tables S5 and S6, respectively).

As an additional analysis we also combined both cohorts in view of the limited number of cases to look at the BPV indices and AUROC derived from that combined cohort. The results derived from that analysis are shown in Tables S7 through S10. AUROC of SD-day SBP was found to be the best BPV index to detect ATF in the combined cohort as well.

Discussion

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 some[18,20] 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.

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.[29,30] Generally, the magnitude of changes in SBP is greater than changes in DBP during gravitational stress.[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.[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[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 indication and support the use of SD-day SBP as a simple screening tool for autonomic failure. However, future prospective studies are needed to confirm the role of SD-day SBP and other BPV markers to detect autonomic failure.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1

Supplemental Methods

Indices of Blood Pressure Variability

Standard deviation (SD)

Standard deviation is 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 [2]. 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.

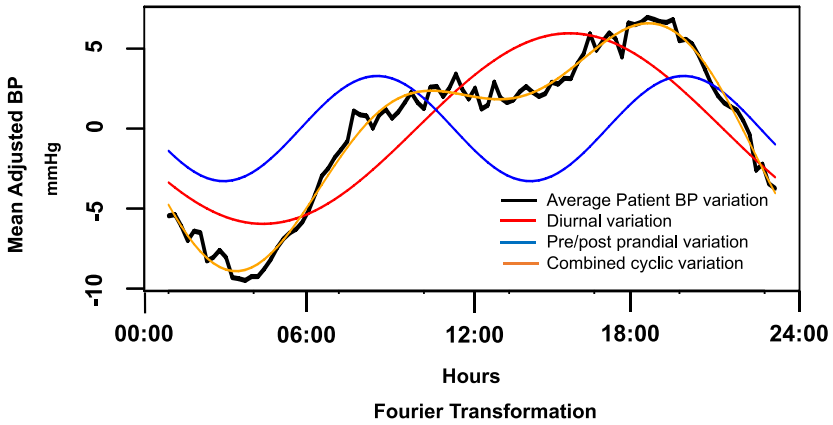


Figure: Black Line: Difference of BP at specific time point from the overall group mean of all patients. Redline: Diurnal group variability pattern for all patients. Blue line: Postprandial BP variation for whole group. Orange line: combined cyclic variation which represents combined effect of both red 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].

$$\text{ARV} = \frac{1}{n-1}\sum_{i=1}^{n-1}\left|x_{i+1} - x_i\right|$$

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(SD) = j + p*ln(mean X), and the parameters "j" and "p" are estimated from this regression analysis. With the estimated parameters, VIM is calculated as:

$$VIM = \frac{SD}{j \times \bar{x}^{p}}$$

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)	**17±7***	14±5	0.02	0.22	0.55	0.40
RSD DBP(mmHg)	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/m$^{2)}$	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±11.7	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.

	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)	21±8	13±5	0.0001
RSD DBP(mmHg)	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.

	Discovery Cohort (n=19)			Validation Cohort (n=13)		
BPV Index	**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.**

	Discovery Cohort (n=19)			Validation Cohort (n=13)		
BPV Index	**Day 1**	**Day 2**	**ICC**	**Day 1**	**Day 2**	**ICC**
SD-Day SBP mmHg	16±6	15±6	0.84	20±10	19±9	0.95
SD-Day DBP mmHg	9±3	9±3	0.72	11±5	12±5	0.95
ARV-Day SBP mmHg	11±4	11±3	0.91	15±7	14±7	0.68
ARV-Day DBP mmHg	7±2	7±2	0.89	10±4	9±3	0.67
CV-Day SBP	0.12±0.04	0.11±0.04	0.80	0.14±0.06	0.14±0.06	0.90
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	0.80	1.33±0.60	1.35±0.63	0.90
VIM-Day DBP mmHg	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		P value
	Cases (n=47)	Controls (n=226)	
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/m$^{2)}$	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.

	Combined Cohort		
Variables	**Cases (n=47)**	**Controls (n=15)**	**P-Value**
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	0.0.09
HR 3 mins post-tilt (bpm)	71±13	78±13	0.07
SBP last reading post-tilt (mmHg)	137±26	128±31	0.0.27
DBP last reading post-tilt (mmHg)	74±14	74±15	1.00
HR last reading post tilt (mmHg)	72±13	82±16	0.0.02

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±8*	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(mmHg)						
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(mmHg)						
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(mmHg)	19±7*	14±5	<0.0001	0.001	0.01	0.01
RSD DBP(mmHg)	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,

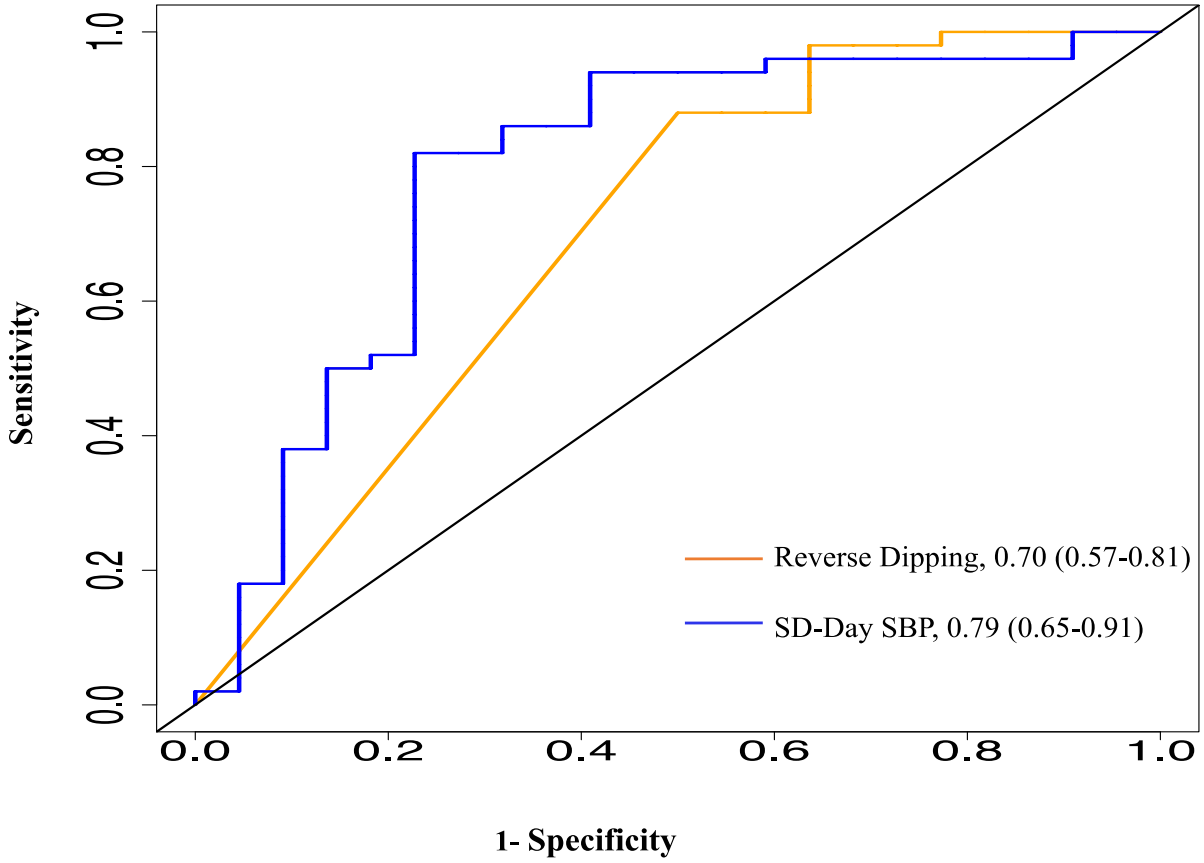
Day = Daytime BP, Night = Nighttime BP. Model 1= Adjusted for age, sex, race, BMI and history of carotid disease. Model 2 = Model 1 + Parkinson's disease, Model 3 = Model 2 + Parkinson's drugs (carbidopa/levodopa or dopaminergic agonist) and BP medications (diuretics, alpha agonist or beta blockers)

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)	
SD-24	0.55 (0.45-0.64)
SD-Day	0.62 (0.53-0.70)
SD-Night	0.64 (0.56-0.72)
ARV SBP(mmHg)	
ARV-24	0.66 (0.57-0.75)
ARV-Day	0.70 (0.61-0.77)
ARV-Night	0.61 (0.52-0.70)
ARV DBP(mmHg)	
ARV-24	0.51 (0.42-0.61)
ARV-Day	0.61 (0.52-0.70)
ARV-Night	0.58 (0.49-0.67)
CV SBP	
CV-24	0.66 (0.57-0.75)
CV-Day	0.72 (0.64-0.81)
CV-Night	0.56 (0.46-0.65)
CV DBP	
CV-24	0.50 (0.42-0.58)
CV-Day	0.62 (0.52-0.70)
CV-Night	0.61 (0.52-0.69)
VIM SBP(mmHg)	
VIM-24	0.67 (0.57-0.76)
VIM-Day	0.72 (0.64-0.80)
VIM-Night	0.57 (0.48-0.66)
VIM DBP(mmHg)	
VIM-24	0.53 (0.60-0.77)
VIM-Day	0.62(0.53-0.71)
VIM-Night	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)

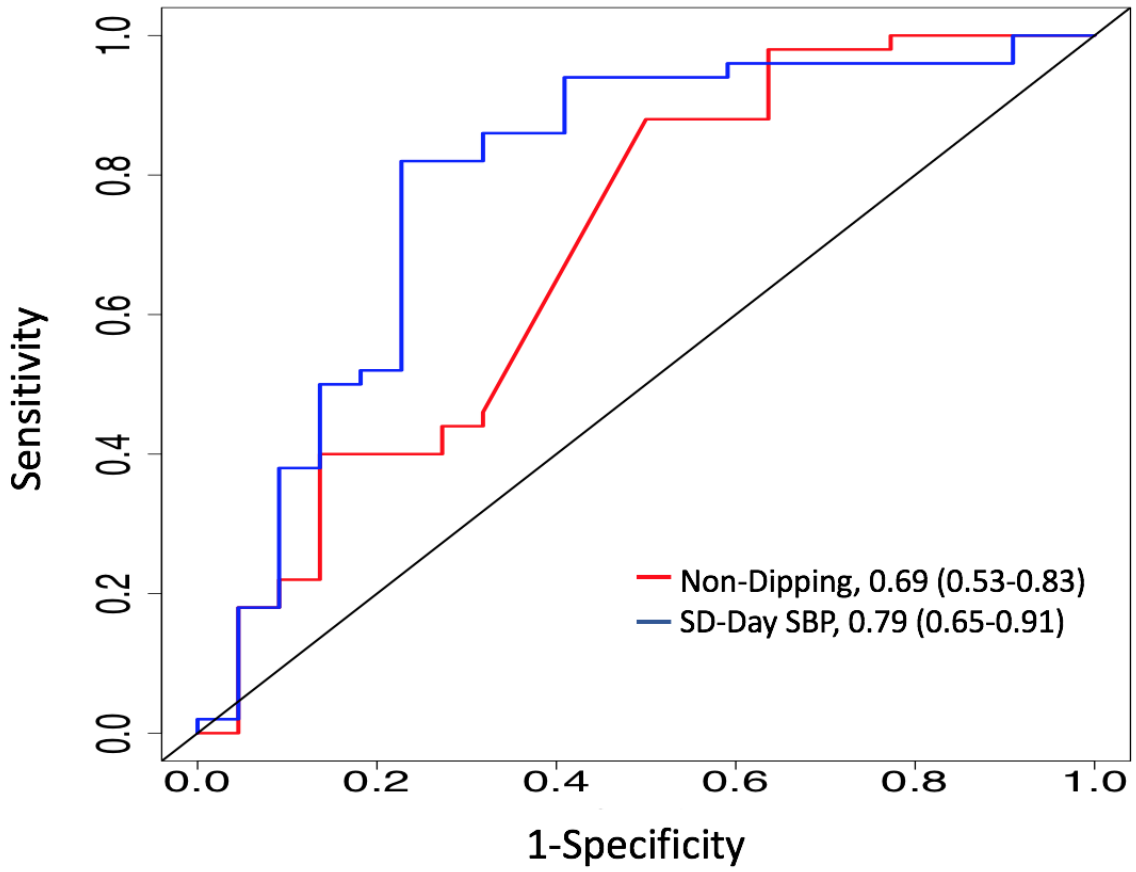
SD=Standard deviation, ARV=Average real variability, CV=Coefficient of variation, VIM=Variation independent of mean, RSD=Residual standard deviation. 24 = 24 hour BP, Day = Daytime BP, Night = Nighttime BP.

Figure S1a. ROC curve comparing reverse nocturnal dipping with standard deviation of daytime (SD-Day) SBP in detecting underlying autonomic failure.



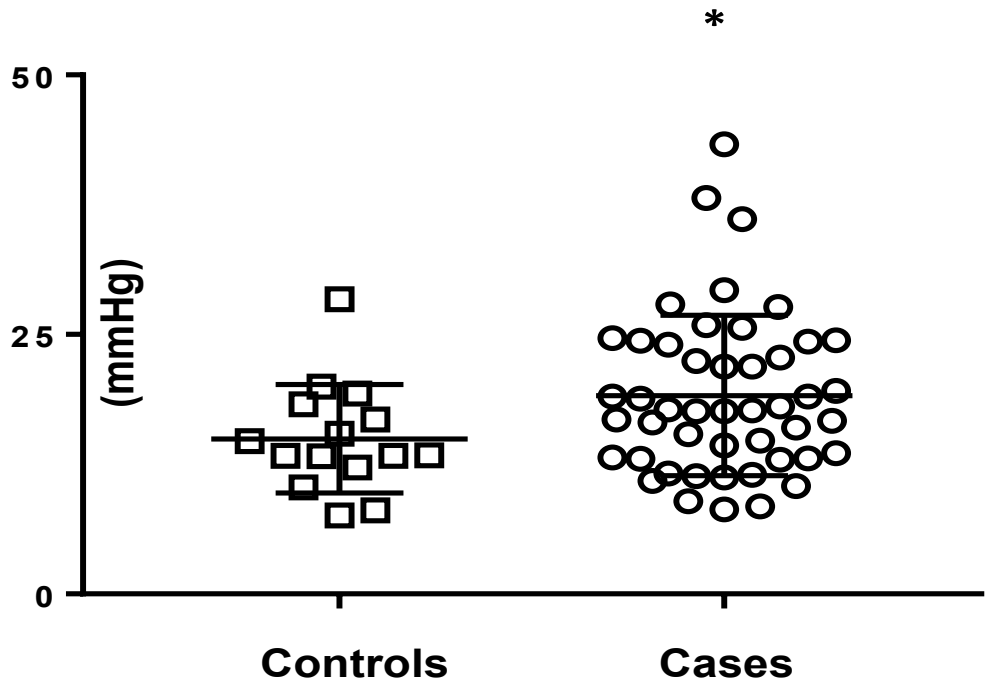
This reveals superior predictive value of SD-Day, over reverse nocturnal dipping.

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.



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