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Twenty-four-hour ambulatory blood pressure and heart rate profiles in diagnosing orthostatic hypotension in Parkinson's disease and multiple system atrophy.

24 hour-ambulatory blood pressure and heart rate profiles in diagnosing orthostatic hypotension in Parkinson's disease and Multiple System Atrophy

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Abstract

Background: 24-hour ambulatory blood pressure and heart rate monitoring (24hr-ABPM) can provide vital information on circadian BP profiles, which are commonly abnormal in Parkinson's disease with and without autonomic failure (PD+AF and PD) and Multiple System Atrophy (MSA). 24hr-ABPM has never been directly compared between MSA, PD and PD+AF with regards to their cardiovascular autonomic function. We aim to determine the usefulness of 24hr-ABPM with diary compared to standard Head-up Tilting (HUT) in diagnosing orthostatic hypotension (OH) in these patient groups.

Methods: 74 patients (23 MSA, 18 PD+AF, 33 PD) underwent cardiovascular autonomic screening following by 24hr-ABPM with diary. Standing tests were included during 24hr-ABPM. The sensitivity and specificity in detecting OH from the 24hr-ABPM standing test was compared with HUT.

Results: During HUT, BP was lower in MSA and PD+AF compared to PD ($p<0.01$) but there was no difference in OH between MSA and PD+AF ($p>0.05$). MSA and PD+AF had a higher proportion of abnormal BP and a reversed BP circadian rhythms compared to those in PD ($p<0.05$) but there was no difference between MSA and PD+AF ($p>0.05$). All patients were divided into those with (OH+) and without OH (OH-) on HUT. Using the standing test during 24hr-ABPM, a SBP fall of >20 mmHg showed a sensitivity and specificity of 82% and 100 % (AUC 0.91, 95% CI 0.84-0.98) in differentiating OH+ from OH-, respectively.

Conclusions: This study demonstrates that PD+AF and MSA patients, with similar OH during HUT, have similar circadian BP patterns. This suggests that autonomic dysfunction influences abnormal BP circadian patterns similarly in these 2 disorders. A high sensitivity and specificity in detecting OH using 24hr-ABPM supports the use of this technique as an adjunct tool for assessing autonomic function in MSA and PD patients.

Introduction

24 hour-ambulatory blood pressure and heart rate monitoring (24 hr-ABPM) is widely used in patients with blood pressure problems, particularly in those with high blood pressure (hypertension). A number of studies have demonstrated the advantage of using this equipment to detect and follow-up patients with hypertension (1-3). More recently, 24 hr-ABPM has also been utilized as a screening test for autonomic dysfunction patients with orthostatic hypotension in conjunction with laboratory tests of autonomic function. Furthermore, 24 hr-ABPM offers information not only on daytime blood pressure (BP) but also circadian BP revealing key information on day- and night-time profiles. In normal subjects, BP is normally lower at night-time which has been described as nocturnal blood pressure 'dipping'. This pattern can be absent or reversed (BP night-time>BP daytime) in patients with autonomic failure, such as Multiple System Atrophy. These patients tend to have lower BP during the day (due to the repeated bouts of OH) and a loss of BP dipping or even a higher BP at night, also influenced by supine hypertension, a common occurrence in autonomic failure (4). According to the latest guidelines from the European Society of Hypertension and the European Society of Cardiology for the management of hypertension, those who have a normal BP reduction at night (BP decrease >10%) are classified as dippers while those with a nocturnal fall of <10% BP are classified as non-dippers. Those patients with a BP increase during the night are grouped as reverse dippers, which are more likely to occur in autonomic failure (5).

24 hr-ABPM is commonly reported as abnormal in patients with Parkinson's Disease (PD) regardless of their underlying autonomic function (6). The prevalence of non-dippers in PD ranges from 48 to 95% (6-8). Abnormal nocturnal circadian falls in blood pressure occur more often in PD+AF compared to PD suggesting that there is a link between abnormal BP circadian rhythms and orthostatic hypotension (8). More recently, 24 hr-ABPM was used among different forms of parkinsonian disorders, including Multiple system atrophy (MSA) and

Progressive supranuclear palsy (PSP) (ref). The results showed that a number of these patients had a significantly higher proportion of absent nocturnal BP dipping compared to age-matched controls. These findings support the use of 24-hr ABPM for screening autonomic function when the autonomic laboratory is not available (6). Nevertheless, 24 hr-ABPM has never been specifically compared in PD patients with and without autonomic failure and MSA patients with autonomic failure. Furthermore, the efficacy of 24 hr-ABPM with an autonomic protocol diary in detecting OH, compared with laboratory head-up tilt-table testing in these patient groups, has also never been evaluated. Such information would help with the often difficult task of differentiating MSA and PD+AF and with the screening of autonomic function in the community setting. The aim of this study was, therefore, to 1) examine 24 hr-ABPM in patients with MSA, PD+AF and PD and 2) determine the usefulness of 24 hr-ABPM compared to standard orthostatic challenge testing (10 minute Head-up Tilt) in diagnosing orthostatic hypotension (OH) in these patients.

Methods

Participants

All patients were recruited from the Autonomic Unit, National Hospital for Neurology and Neurosurgery (NHNN), Queen Square, London, UK between 2004 and 2013. Idiopathic PD (without autonomic failure) patients were diagnosed using the UK Parkinson's Disease Society Brain Bank diagnostic criteria [UK-PDSBB]. PD with autonomic failure (PD+AF) was defined as idiopathic PD with orthostatic hypotension (Systolic/Diastolic blood pressure fall $\geq$ 20/10 mmHg) (9, 10). MSA patients were diagnosed using Gilman's criteria (11) for probable MSA. Only probable MSA patients with orthostatic hypotension were included in the study.

All patients had a good and sustainable response to levodopa treatment without features suggesting atypical parkinsonian disorders. Participants had no previous history of cardiovascular disease (e.g. coronary heart disease, heart failure, cardiac arrhythmia, and hypertension), Diabetes mellitus or other illnesses that could affect autonomic function. PD patients were asked to stop dopaminergic medications and other drugs that could interfere with autonomic function at least 12 hours before autonomic testing.

Patients were selected only if cardiovascular autonomic screening tests (AFT) and 24 hr-ABPM were performed during the same admission. In order to verify the efficacy of 24 hr-ABPM in detecting OH using an autonomic diary protocol, only patients who completed a diary as part of the test were included in the sensitivity analyses.

Clinical history and evaluation of autonomic nervous system function

Demographic data, such as age at testing, dopaminergic medications and disease duration were also noted.

Cardiovascular autonomic screening tests (AFT)

All patients underwent screening autonomic function tests (AFT) using the Autonomic Unit Queen Square protocols (12) to ascertain whether or not patients had orthostatic hypotension (OH) and autonomic failure (AF). More info needed here on HUT etc.

24 hour-Ambulatory Blood Pressure and Heart Rate Monitoring (24 hr-ABPM)

All patients were fitted with the 24 hr-ABPM (model 90207, Spacelabs™ Medical, Redmond, Washington) after their AFT as part of their autonomic investigations. BP and HR were recorded every 20 minutes during the day (0800-2300) and every 60 minutes during the night (2300-0800). The average BP and HR were calculated for daytime, night-time and the entire 24-hour period. Patients were asked to record their symptoms in the diary during the day (e.g.

dizziness, light-headedness, blurred vision etc) as well as the position and activity (lying down, sitting, standing, walking, and exercising) at the same time. Patients were also asked to record additional BP readings in addition to the automated readings if they developed symptoms. Bed- and wake-up time were also recorded in order to determine the period of sleep. Postural challenges were included in the diary for patients to complete during the 24 hr-ABPM monitoring. These included an orthostatic challenge using a 5-minute standing test. Patients were asked to press a recording button after 5-minute of lying down and again after 5-minute standing 4 times throughout the 24 hours (when?). Symptoms (if experienced by patients) were also noted in the diary. BP and HR variability were derived from the standard deviations of the means of the specific period of times (24-hr, daytime and night-time).

Patients were classified into 3 groups: dipper (BP fall during night-time>10% compared to daytime), absent nocturnal BP fall or non-dipper (BP fall during night-time<10% compared to daytime) and reverse nocturnal BP (BP higher during night-time than daytime). Patients with an average daytime SBP >140 mmHg or DBP >90 were defined as daytime hypertensives and those with nighttime SBP >125 or DBP >75 as nighttime hypertensives according to international guidelines (13).

Statistical Analyses

Data are presented as mean (± 1 SD) or median (inter-quartile range), where appropriate. Analysis of covariance (ANCOVA) was used for comparisons between the 3 groups for normally distributed data while the Kruskal-Wallis test was used if data were non-normally distributed. If there was a significant difference, Mann-Whitney U tests were then used to compare between 2 groups for non-normally distributed data and unpaired t-tests for normally distributed data with Bonferroni corrections. Chi-square analyses were used for analysis of categorical variables.

SBP and DBP responses from the 24 hr-ABPM standing test with the greatest degree of BP reduction were compared with the BP and HR responses during HUT using a standard criteria of OH (SBP fall $\geq$20 mmHg or DBP fall $\geq$10 mmHg). Considering the BP responses during HUT as a gold standard test, sensitivity (Sn) of the 24 hr-ABPM to detect OH was defined as the proportion of patients who met the criteria of OH from a standing test during 24 Hr monitoring and the proportion of patients who met the criteria of OH during laboratory HUT. Specificity (Sp) was defined as the proportion of patients who did not meet the criteria of OH in the standing test in 24 Hr monitoring and all patients who were correctly classified as not having OH from HUT. ROC (Receiver operating characteristic) analysis was used to evaluate the sensitivity and specificity in detecting OH from 24 hr-ABPM and to calculate Sn and Sp using different BP cut-off points. In general, the optimal cut-off point would be both Sn and Sp as close to 100% as possible. Nonetheless, it is less likely to happen as the Sn tends to vary inversely with Sp (Sn increases as Sp decreases, or vice versa). In this study, ROC curves were plotted as Sn against 1-Sp and were used to determine the Sn and Sp of the 24 hr-ABPM in detecting a fall of 20-mmHg SBP and 10-mmHg DBP (according to the standard OH diagnostic criteria).

The area under the curve (AUC) of the 24 hr BP profile was also calculated (how?). The AUC is an overall summary of the diagnostic performance of a test. The perfect discrimination for AUC is 1, which means the diagnostic test can perfectly differentiate between two conditions with both Sn and Sp equalling 100%. An AUC of 0.9 or higher represents an outstanding discrimination. A value of 0.8-0.9 shows excellent discrimination and a value of 0.7-0.8, acceptable discrimination. An AUC of 0.5 or less indicates that the diagnostic accuracy is questionable and not different from random chance. Statistical analyses were carried out using STATA 11.0 (STATA Corporation, College station, Texas, USA). All tests were 2-sided and a p value of $\leq$0.05 was considered significant.

Results

Demographic data

74 patients (23 MSA, 18 PD+AF, 33 PD) were included in the analyses. Patients with PD+AF were significantly older than PD and MSA (both $p<0.01$) but there was no difference in age between MSA and PD ($p=0.55$). There was no difference in disease duration among groups ($p=0.23$). Dopaminergic treatment was more commonly used in patients with PD and PD+AF compared to those with MSA (MSA vs. PD+AF; $p=0.01$ and MSA vs. PD; $p<0.01$). There was no difference in the number of patients on dopaminergic medication among PD and PD+AF ($p=0.53$, Table 1).

Table 1. Patient demographic data

Variable	MSA	PD+AF	PD
Number	23	18	33
% Male	48	44	67
Age at testing; Mean (SD), yrs	62±9	72±7*$	64±10
Disease duration; Median (IQR), yrs	4 (3-6)	7 (4-10)	6 (2-10)
% Dopaminergic treatment	39*#	78	85
Values are mean±SD unless stated, * $p<0.05$ vs. PD, # $p<0.05$ vs. PD+AF, $ $p<0.05$ vs. MSA			

Cardiovascular responses to HUT

Supine SBP and DBP were not significantly different between MSA, PD+AF, PD patients but there was a higher baseline HR in MSA patients. During head-up tilting (HUT), SBP was significantly lower in patients with MSA and PD+AF compared to PD ($p<0.01$). Correspondingly, BP changes during HUT were significantly higher in MSA and PD+AF when

compared to PD. There were no difference in SBP and DBP during HUT between MSA and PD+AF (p=0.35 and p=0.90, respectively) but HR was significantly higher in MSA during HUT (Table 2). During HUT, all patients with MSA and PD+AF fulfilled the criteria of OH, whereas none of the PD patients met the criteria of OH during HUT.

Table 2. Blood pressure and HR during supine and head-up tilting and orthostatic changes in MSA, PD+AF and PD patients

Variable	MSA (n=17)	PD+AF (n=11)	PD (n=16)
HUT			
Supine SBP	137±18	140±21	130±14
Supine DBP	81±11	75±15	75±10
Supine HR	77±9	69±4$^{\$}$	69±10$^{\$}$
Tilt SBP	95±19*	101±24*	126±16
Tilt DBP	60±13*	63±17*	76±10
Tilt HR	85±13	77±6$^{\$}$	76±11$^{\$}$
Orthostatic ΔSBP	-42±17*	-39±17*	-5±8
Orthostatic ΔDBP	-20±12*	-12±10*	0±5
Orthostatic ΔHR	8±6	8±5	7±5
Values are mean±SD unless stated, *p<0.05 vs. PD, $^{\$}$p<0.05 vs. MSA			

24 hour-Ambulatory BP Monitoring data

MSA patients had significantly lower daytime SBP and DBP compared to PD patients (both p<0.01), whereas there was no difference between PD+AF and PD patients (p=0.34), as well as between MSA and PD+AF (p=0.17). Daytime average HR was not different among patient groups (p=0.28). During nighttime, there was a significantly higher SBP in PD+AF patients compared to PD (p=0.01), but no difference between MSA and PD (p=0.17) or MSA and PD+AF (p=0.11). Nighttime HR in MSA was greater than PD (p=0.03) but there was no difference between PD and PD+AF (p=0.06). The average SBP, DBP and HR in the 24-hour period were not different among groups (p>0.05).

There were no differences in the number of patients with daytime and nighttime hypertension among groups ($p>0.05$). The sizes of the nocturnal blood pressure change in SBP and DBP were significantly lower in MSA compared to PD (both $p<0.01$) but there was no difference between MSA and PD+AF (SBP; $p=0.71$ and DBP; $p=0.55$). The size of the nocturnal HR fall was not different among patient groups ($p=0.06$). Correspondingly, MSA and PD+AF had a higher proportion of patients with abnormal BP circadian rhythms (both absent and reversed BP circadian rhythms; non-dippers) than patients with PD ($p<0.01$ and $p=0.04$, respectively) but not between MSA and PD+AF ($p=0.08$). Patients with reversed BP circadian rhythms were significantly more common in MSA and PD+AF compared to those with PD (both $p<0.01$) but not between MSA and PD+AF ($p=0.14$). There was also no difference in the number of patients with an absent BP circadian rhythm among groups ($p>0.05$; Table 3).

Table 3. 24 hr-ABPM profiles in MSA, PD and PD+AF

Variable	MSA (n=23)	PD+AF (n=18)	PD (n=33)
Daytime			
- Mean SBP	116±12*	122±13	127±12
- Mean DBP	71±7*	73±12	77±9
- Mean HR	81±9	75±7	79±10
Patients with daytime hypertension, % (n)	4% (1/23)	6% (1/18)	18% (6/33)
Nighttime			
- Mean SBP	119±12	127±16*	115±12
- Mean DBP	70±9	72±13	67±9
- Mean HR	72±11*	65±8	66±8
Patients with nighttime hypertension, % (n)	30% (7/23)	50% (9/18)	24% (8/33)
24-hour values			
- Mean SBP	117±11	123±13	125±11
- Mean DBP	71±6	72±11	76±9
- Mean HR	80±9	73±7	76±9
Patients with abnormal BP circadian rhythm, % (n)	96% (22/23)*	78%(14/18)*	48% (16/33)
Patients with absent BP circadian rhythm, % (n)	39% (9/23)	22%(4/18)	33% (11/33)
Patients with reversed BP circadian rhythm, % (n)	57% (13/23)*	56%(10/18)*	15% (5/33)
Mean Nocturnal BP/HR change			
- SBP (%)	+2.8 ±9.0*	+4.3 ±14.7*	-9.1 ±8.9
- DBP (%)	-1.6 ±10.8*	-0.1 ±20.7*	-12.9 ±11.0
- HR (%)	-11.1±9.9	-12.7±5.7	-16.1±7.3
Values are mean±SD unless stated, * $p<0.05$ vs. PD, $^{\#}$ $p<0.05$ vs. PD+AF, $^{\$}p<0.05$ vs. MSA			

24-hr SBP variability was significantly higher in MSA and PD+AF patients compared to PD (both $p<0.01$) but there was no difference in 24-hr DBP variability between MSA and PD+AF ($p=0.32$). There was a significantly lower daytime DBP variability in PD+AF compared to PD. MSA patients had significantly lower 24-hr HR variability compared to PD ($p<0.01$). SBP, DBP and HR variability during nighttime were not different among groups ($p>0.05$; Table 4).

Table 4. 24 hr-ABPM BP and HR variability in MSA, PD and PD+AF

Variable	MSA (n=23)	PD+AF (n=18)	PD (n=33)
BP variability			
Daytime			
- SBP	15.6±5.2*	16.8±4.9*	11.6±4.4
- DBP	10.0±2.9	10.8±2.8*	8.9±2.6
- HR	6.7±2.7*	7.8±2.9	9.3±3.2
Nighttime			
- SBP	11.2±6.4	12.8±5.3	9.5±4.1
- DBP	7.9±3.6	7.8±3.1	7.3±3.0
- HR	4.4±2.2	5.5±2.7	4.8±2.4
24-hr			
- SBP	15.5±4.5*	17.2±4.5*	13.1±4.6
- DBP	10.2±2.3	11.2±2.7	9.9±3.0
- HR	7.5±2.8*	8.4±2.6	10.2±2.9

Values are mean±SD, * $p<0.05$ vs. PD, # $p<0.05$ vs. PD+AF, $ $p<0.05$ vs. MSA

SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure; values in mmHg, Heart Rate=HR; value in bpm.

24 hr-ABPM and patient-report diary

Out of 74, 44 (59%) patients completed the diary during the 24 hr-ABPM monitoring. There was no difference in the number of patients who completed the diary among groups; 17(74%) MSA, 11(61%) PD+AF and 16 (48%) PD patients. For the purpose of the sensitivity and specificity analyses of 24 hr-ABPM in detecting OH, patients were divided into those with and those without OH according to the BP responses during HUT. MSA and PD+AF patients were combined as a single group (OH+ group) and PD patients were a control group (OH-). The average supine SBP was significantly higher in patients with OH (OH+), but the mean DBP and HR were not different compared to patients without OH (OH-). During head-up tilting (HUT), SBP was significantly lower in OH+ compared to OH- ($p<0.01$). By definition, the

degree of SBP and DBP changes during HUT were significantly higher in OH+ compared with OH- ($p<0.01$).

Cardiovascular responses to HUT and standing test using ABPM

With 24 hr-ABPM, supine SBP, DBP and HR were not different between OH+ and OH- but the average SBP and DBP were significantly lower in OH+ during the standing test compared to OH-. The degree of orthostatic changes (both SBP and DBP) were also significantly different between OH+ and OH- ($p<0.05$) but not for HR (Table 5). Was OH lower during the stand test?

Table 5. Blood pressure and HR during supine, head-up tilting and orthostatic changes in patients without OH (PD) compared with patients with OH (MSA and PD+AF)

Variable	Patients with OH (MSA and PD+AF)	Patients without OH (PD)
Number of patients	28	16
HUT		
Supine SBP	138±16$^{£}$	127±13
Supine DBP	79±11	74±9
Supine HR	73±8	70±7
Tilt SBP	100±19$^{\phi£}$	125±17
Tilt DBP	63±13$^{\phi£}$	75±8
Tilt HR	81±12$^{\phi}$	78±9
ΔSBP	-38±15$^{£}$	-3±9
ΔDBP	-16±11$^{£}$	1±5
ΔHR	8±6	8±4
Standing test		
Supine SBP	128±16	128±18
Supine DBP	75±13	74±11
Supine HR	74±11	74±10
Stand SBP	99±14$^{\phi£}$	122±16
Stand DBP	62±11$^{\phi£}$	78±12
Stand HR	84±12$^{\phi}$	81±11
ΔSBP	-29±19$^{£}$	-6±6
ΔDBP	-13±13$^{£}$	4±6
ΔHR	10±7	7±5
Values are mean±SD, $^{£}$ $p<0.01$ vs. patients without OH, $^{\phi}p<0.01$ vs. corresponding Supine		

ROC analysis for detecting OH during HUT and standing tests using ABPM with autonomic protocol diary.

Using 24 hr-ABPM, the area under the curve (AUC) that distinguishes OH+ from OH- was 0.87 (95% CI, 0.75-0.99). A fall of 20 mmHg or more in SBP showed a sensitivity and specificity of 82% and 100% (AUC 0.91, 95% CI 0.84-0.98) in differentiating OH+ from OH-, respectively. A DBP fall of 10 mmHg or more had a 57% sensitivity and a 94% specificity to discriminate OH+ from OH- with an AUC of 0.75 (0.64-0.87; Table 6). A 20 mmHg systolic BP fall criteria had a significantly higher efficacy in detecting OH compared to a 10-mmHg DBP fall using the 24 hr-ABPM with the autonomic protocol diary ($p<0.01$).

Table 6. Sensitivity analysis for 24 hr-ABPM in detecting orthostatic hypotension (OH)

	Sensitivity (%)	**Specificity (%)**	**AUC (95% CI)**
BP *- SBP fall $\geq$ 20 mmHg* *- DBP fall $\geq$ 10 mmHg*	 82 57	 100 94	 0.91 (0.84-0.98) 0.75 (0.64-0.87)

Discussion

The aim of this study was to 1) examine 24 hr-ABPM in patients with chronic autonomic failure (MSA+AF, PD+AF and PD) and 2) determine the effectiveness of 24 hr- ABPM compared to standard orthostatic challenge testing (10 minute Head-up Tilt) in diagnosing orthostatic hypotension (OH) in these patients. The main findings in this study were that an abnormal circadian BP rhythm (either a blunted nocturnal fall of BP or a reversed nocturnal fall) occurred in about half of the patients with PD. This proportion was higher in PD+AF and in patients with MSA. In comparison to a recent study (6), the prevalence of an abnormal circadian BP rhythm in PD in the present study was similar whereas the prevalence of an abnormal circadian BP rhythm in MSA patients in the present study was higher (68% vs. 96%, respectively). These inconsistent MSA results may be explained by the fact that this study categorized patients with regards to a patient's diagnosis *and* their autonomic function, whereas the previous study used only a diagnostic category (e.g., MSA patients without autonomic failure were included). Furthermore, a reversed nocturnal circadian BP pattern was more common in autonomic failure patients, presenting in more than 50% of MSA and PD+AF patients compared to only 15% in PD patients. These findings suggest that even though a blunted nocturnal fall in 24-hr BP profiles can often be seen among PD patients without autonomic failure, a reversed nocturnal circadian BP pattern is much more common in patients with autonomic failure (PD+AF and MSA). Daytime SBP variability was also higher in patients with autonomic failure, which could be due to greater fluctuations in BP in MSA and PD+AF during daily activities compared to patients without autonomic failure, and supports the idea that this value could also be an additional useful measurement in 24 hr-ABPM in patients with suspected autonomic failure and/or orthostatic hypotension. The 24-hr BP profiles in patients with MSA and PD+AF were relatively similar suggesting that 24 hr-ABPM patterns cannot be used to discriminate between MSA and PD+AF.

Human circadian rhythms are controlled by the suprachiasmatic nucleus (SCN) in the hypothalamus (14). The SCN projects afferent input to the paraventricular nucleus (PVN), which plays an important role in controlling various autonomic functions, such as stress responses and metabolism (15). Both sleep and physical activity have a large influence on BP and HR circadian changes, including the normal physiological blood pressure fall during sleep (16). Although the cause of abnormal circadian BP rhythms in PD and MSA remains unclear, the involvement of SCN and PVN are likely to play an important contributing role (17). An abnormal circadian BP rhythm in MSA is supported by prior pathological studies showing pathological changes within both the paraventricular nucleus (18) and the suprachiasmatic nucleus (19) in MSA. In contrast to MSA, the neuronal loss and pathological involvement in these structures have never been reported in PD and PD+AF. Nevertheless, sleep dysfunction is common in both patients with PD and MSA. The major cause of this problem includes REM (Rapid Eye Movement) sleep behavior disorder (RBD), obstructive sleep apnea (OSA) and excessive daytime somnolence (EDS). These features may partly explain the reason why abnormal circadian BP profiles frequently occur in both disorders. Although abnormal circadian BP rhythms are common in PD, PD+AF and MSA, it is important to note that the number of patients with a reversed circadian BP profile at night was significantly higher in PD+AF and MSA compared to PD (without AF). This finding suggests that autonomic dysfunction plays an important contributing role in the control of circadian BP rhythms. Supine hypertension is a common feature in patients with autonomic failure (20) and is also associated with OH (e.g., the severity of autonomic failure) (4). It is thus very likely that supine hypertension contributed to the reversed circadian BP pattern in MSA and PD+AF patients in the present study. The cause of supine hypertension in MSA has been suggested to result from an inappropriate residual sympathetic tone (21). These findings also emphasize that the

reversed circadian BP pattern from 24 hr-ABPM is a shared phenomenon in both patients with autonomic failure from both pre- (MSA) and post-ganglionic (PD) lesions, rather than a disease-specific feature.

The present study also showed that using an autonomic protocol diary alongside 24 hr-ABPM is useful for helping diagnose patients with OH. Using the standard criteria of OH, this technique provides a reasonably high sensitivity (82%) and specificity (100%) to distinguish OH+ from OH- patients with parkinsonism. Nevertheless, a 20-mmHg fall of SBP has a significantly better efficacy in detecting OH from 24 hr-ABPM when compared with a 10-mmHg fall of DBP. To date, there has been no study that has used a diary with 24 hr- ABPM to investigate patients with OH. Given that these are non-invasive, relatively simple tests to perform without a requirement of an autonomic laboratory, this technique should be included as part of autonomic investigations in suspected OH workups. An adjunct diary to 24 Hr BP monitoring can also provide additional information with regards to the effect of patient activities on BP and HR and their relation to symptoms. Such an approach would allow the clinician/scientist to make a connection between activities and BP/HR during events if symptoms develop (22). 24 hr-ABPM can also be used to monitor BP and HR in patients with OH/autonomic failure after starting anti-hypotensive medications.

In conclusion, this study demonstrated that patients with PD+AF and MSA, who had a similar degree of orthostatic hypotension during HUT, generally have similar circadian BP and HR patterns as revealed by 24 hr-ABPM. As abnormal circadian rhythms are similarly present in PD+AF and MSA, this suggests that the proportion of abnormal BP circadian patterns (both absent and reversed BP circadian rhythm) in 24 hr-ABPM depends on the autonomic function

rather than the diagnosis. Moreover, this study also, for the first time demonstrated that 24 hr-ABPM can offer more information regarding OH in patients with autonomic failure if a patient-completed autonomic protocol diary containing postural challenges (standing) are used. This approach has reasonably high sensitivity and specificity in detecting OH.

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