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RESEARCH ARTICLE

Frequency of Orthostatic Hypotension in Isolated REM Sleep Behavior Disorder

The North American Prodromal Synucleinopathy Cohort

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Abstract

Background and Objectives

Although orthostatic hypotension (OH) can be an early feature of autonomic dysfunction in isolated REM sleep behavior disorder (iRBD), no large-scale studies have examined the frequency of OH in iRBD. In this study, we prospectively evaluated the frequency of OH in a large multicenter iRBD cohort.

Methods

Participants 18 years or older with video polysomnogram-confirmed iRBD were enrolled through the North American Prodromal Synucleinopathy consortium. All participants underwent 3-minute orthostatic stand testing to assess the frequency of OH, and a Δ heart rate/Δ systolic blood pressure (ΔHR/ΔSBP) ratio <0.5 was used to define reduced HR augmentation, suggestive of neurogenic OH. All participants completed a battery of assessments, including the Scales for Outcomes in Parkinson Disease-Autonomic Dysfunction (SCOPA-AUT) and others assessing cognitive, motor, psychiatric, and sensory domains.

Results

Of 340 iRBD participants (65 ± 10 years, 82% male), 93 (27%) met criteria for OH (ΔHR/ΔSBP 0.37 ± 0.28; range 0.0–1.57), and of these, 72 (77%) met criteria for OH with reduced HR augmentation (ΔHR/ΔSBP 0.28 ± 0.21; range 0.0–0.5). Supine hypertension (sHTN) was present in 72% of those with OH. Compared with iRBD participants without OH, those with OH were older, reported older age of RBD symptom onset, and had worse olfaction. There was no difference in autonomic symptom scores as measured by SCOPA-AUT.

Discussion

OH and sHTN are common in iRBD. However, as patients may have reduced autonomic symptom awareness, orthostatic stand testing should be considered in clinical evaluations. Longitudinal studies are needed to clarify the relationship between OH and phenoconversion risk in iRBD.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Coinvestigators are listed at links.lww.com/WNL/D242.

Glossary

ART = autonomic reflex testing; **BP** = blood pressure; **bpm** = beats per minute; **BSIT** = Brief Smell Identification Test; **DBP** = diastolic blood pressure; **DLB** = dementia with Lewy bodies; ***DSM-V*** = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; **FM-100** = Farnsworth Munsell 100 Color Hue test; **HR** = heart rate; **HUTT** = head-up tilt table; **IQR** = interquartile range; **IRB** = institutional review board; **iRBD** = isolated RBD; **MLR** = multiple linear regression; **MoCA** = Montreal Cognitive Assessment; **MSA** = multiple system atrophy; **NAPS** = North American Prodromal Synucleinopathy; **nOH** = neurogenic OH; **OH** = orthostatic hypotension; **PAF** = pure autonomic failure; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder; **SBP** = systolic blood pressure; **SCOPA-AUT** = Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; **sHTN** = supine hypertension; **SNRI** = selective serotonin norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **vPSG** = video polysomnogram.

Trial Registration Information

ClinicalTrials.gov: NCT03623672; North American Prodromal Synucleinopathy Consortium.

Introduction

REM sleep behavior disorder (RBD) is a disorder characterized by the loss of skeletal muscle atonia during REM sleep with dream enactment behavior.[1,2] Longitudinal studies have demonstrated that isolated RBD (iRBD), or RBD in the absence of Parkinson disease (PD), multiple system atrophy (MSA), or dementia with Lewy bodies (DLB), is often a prodromal manifestation of one of these disease states.[3-5] However, the rate of phenoconversion, that is, conversion from iRBD to clinically manifest synucleinopathy, is variable, with the prodromal period lasting years to decades[6-8] and biomarkers that predict the subtype of synucleinopathy in patients with iRBD are lacking. To better inform prodromal biomarker selection and prepare for future clinical trials, the North American Prodromal Synucleinopathy (NAPS) consortium was established in 2018. NAPS is a multicenter longitudinal observational study across 10 coordinated sites in the United States and Canada, with the goal of enrolling 360 participants with iRBD over 3 years.

Autonomic dysfunction represents 1 potential biomarker, as it is present in all synucleinopathies[9] and commonly emerges in prodromal disease stages, such as iRBD. In our experience, orthostatic hypotension (OH) is one of the most common manifestations of autonomic dysfunction in these populations. It is defined as a sustained decrease in systolic blood pressure (SBP) of ≥20 mm Hg and/or diastolic blood pressure (DBP) of ≥10 mm Hg within 3 minutes of standing or head-up tilt table (HUTT) testing.[9] Non-neurogenic factors contributing to OH are common with advancing age[10] and include hypovolemia, bedrest, medications, heart failure, anemia, and severe varicose veins, among others.[11] Neurogenic OH (nOH) is less common and highly correlated with the presence of an underlying autonomic disorder, resulting in impaired norepinephrine release from postganglionic sympathetic nerves.[12,13] As this denervation can also affect cardiac autonomic innervation to the sinoatrial node,[14] many individuals with nOH fail to mount an appropriate compensatory tachycardia in the setting of significant decrements in BP.[15] nOH is quite common in the synucleinopathies, affecting an estimated 30%–50% of individuals with PD,[16] 69% of individuals with DLB,[17] and 70%–80% of individuals with MSA.[18,19] The frequency of OH and nOH has not been reported in large-scale iRBD studies. Diagnosing OH in general and nOH in particular is important in iRBD as it not only helps inform the underlying pathology of alpha-synuclein but also informs prognosis, as nOH has a much worse prognosis than non-nOH.[12]

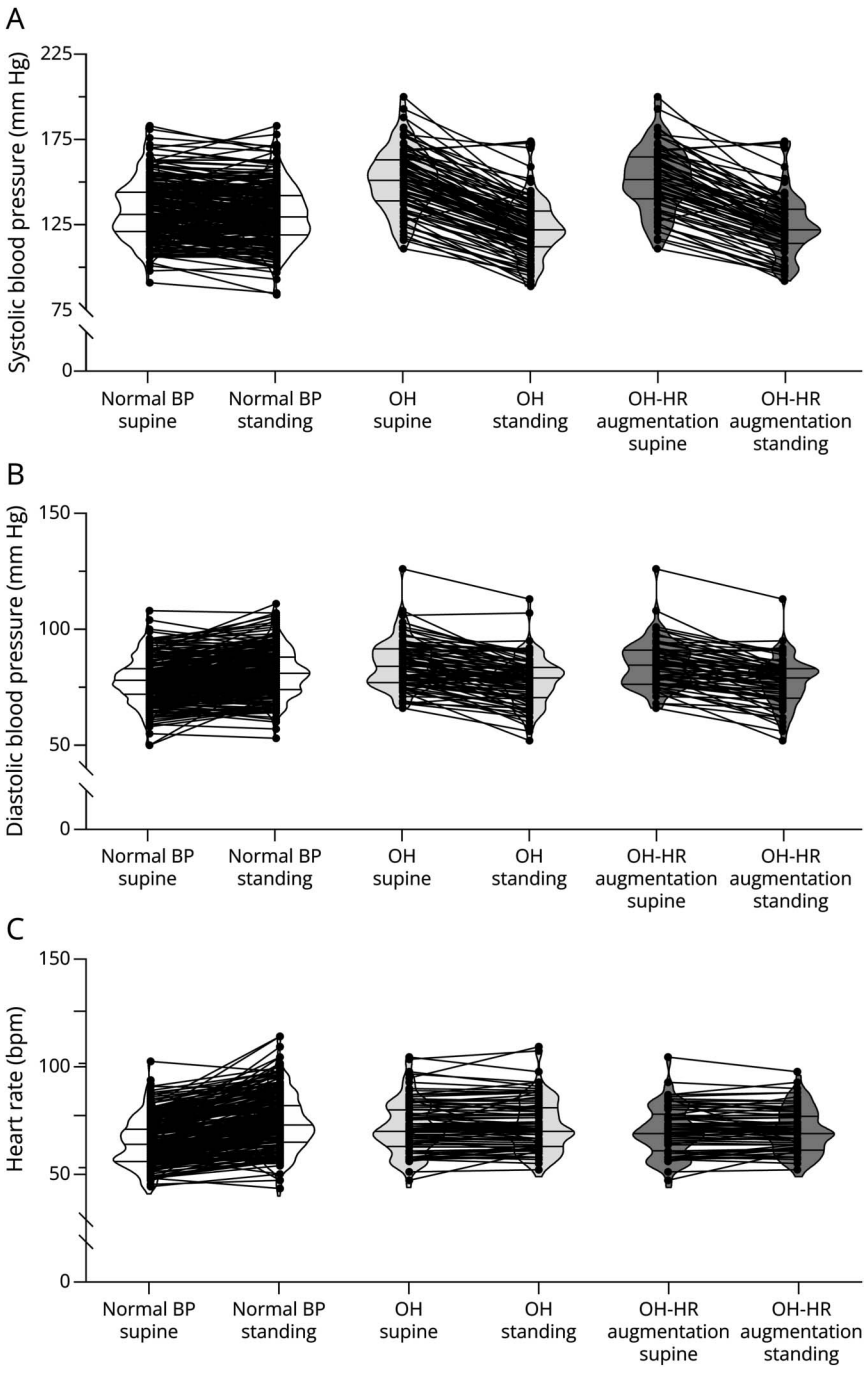
Although its application to prodromal synuclein states, such as iRBD, requires validation, calculation of the ΔHR/ΔSBP ratio (ratio of increase in heart rate [HR] in beats per minute [bpm]/change in SBP in mm Hg on standing) has been recently demonstrated to provide excellent sensitivity (91.3%) and specificity (88.4%) distinguishing nOH from non-nOH (area under the curve 0.96, $p < 0.0001$) in a population of patients with autonomic failure.[15] We applied this methodology to estimate the frequency of nOH in iRBD to better understand the neurologic characteristics of these individuals in the NAPS baseline cohort. These findings will help neurologists, sleep specialists, and other practitioners evaluating patients with iRBD to accurately characterize potential disease trajectory markers for future clinical trials and may present an opportunity to intervene with symptomatic treatments for OH, a condition associated with significant morbidity and mortality.[20]

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The NAPS Consortium protocol is a prospective comprehensive battery of demographic, neurocognitive, motor, sensory, autonomic, and other clinical features of participants with

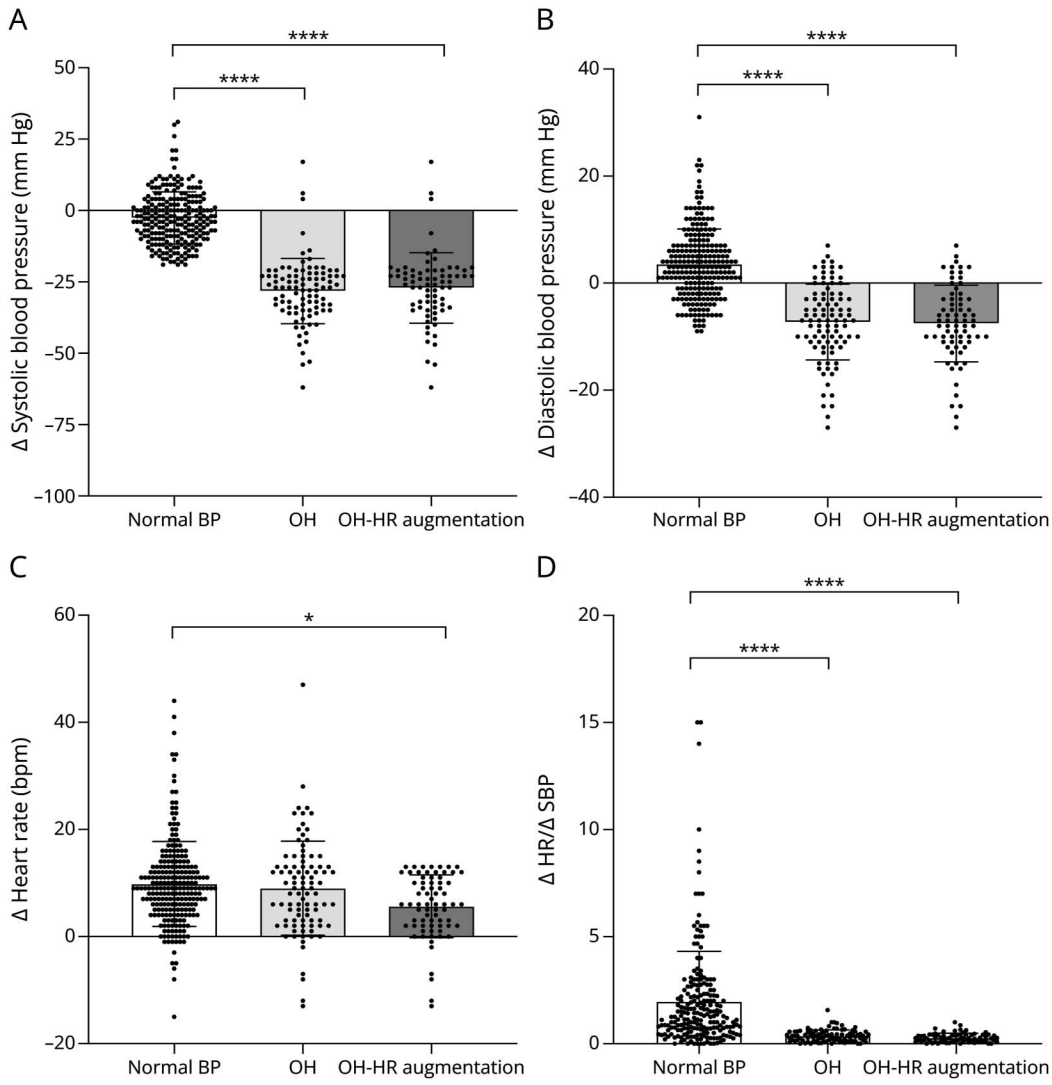
Figure 1 Systolic and Diastolic Blood Pressure



Systolic (A) and diastolic (B) BPs as well as heart rate (C) when supine and after standing between the normal BP group (open violin plot), OH (light shaded violin plot), and OH-HR augmentation (heavy shaded violin plot). Individual data points and connecting supine vs standing outcomes are plotted. The center line for each violin plot represents the mean with 75% and 25% quartiles above and below, respectively. Each plot is unsmoothed extended from min to max, reflecting an overall cohort distribution. *$p < 0.05$. BP = blood pressure; HR = heart rate; OH = orthostatic hypotension.

iRBD. Clinical trials registered (NCT03623672) as NAPS. A detailed description of the NAPS cohort and study design has been previously described.[21] Participants were 18 years or older with overnight video polysomnogram (vPSG)–confirmed RBD by *International Classification of Sleep Disorders-3* criteria[e1] and did not meet criteria for PD,[e2] DLB,[e3] MSA,[e4] narcolepsy,[e5] or any other disorder associated with RBD. Cross-sectional data from NAPS Consortium participants recruited between August 2018 and April 2021 from 9 sites across North America were included in this analysis: Washington University School of Medicine in St. Louis (20171205), Mayo Clinic Rochester (18-004722 00), University of Minnesota (study00003927), Center of Advanced Research in Sleep Medicine at the Hôpital du Sacré-Coeur de Montréal (MP-32-2019-1652), Massachusetts General Hospital/Harvard University (2018P002080), Emory University (104229), University of California Los Angeles (18-000801), Stanford University (53655), and the Veteran Affairs Portland Health Care System (STUDY00020615 via Oregon Health & Science University). This study was performed according to the Declaration of Helsinki and approved

Figure 2 Change in SBP/DBP and HR



Changes in SBD (A), DBP (B), HR (C), and the ΔHR/ΔSBP ratio (D) are presented. The open, light-shaded and heavy-shaded bars reflect the mean value for the normal BP group, OH, and OH-HR augmentation participants, respectively, with standard deviation error bars extending above/below. All individual data points are presented for transparency. *$p < 0.05$. BP = blood pressure; DBP = diastolic blood pressure; HR = heart rate; OH = orthostatic hypotension; SBP = systolic blood pressure.

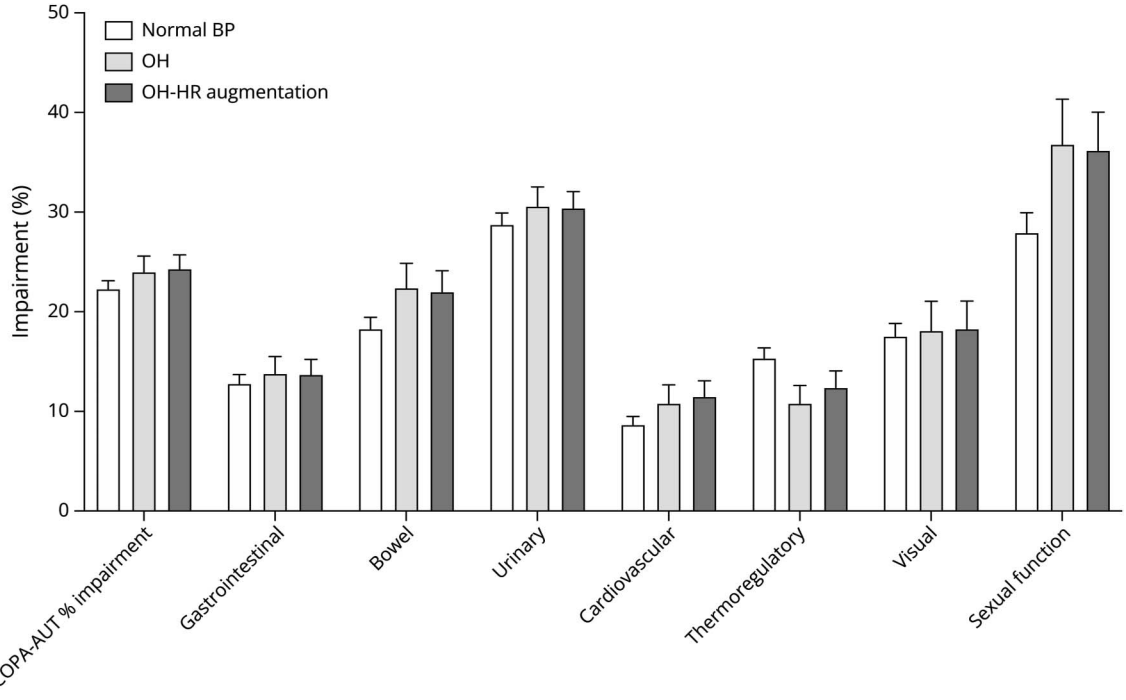
by the institutional review board (IRB) from each enrolling site (corresponding local IRB approval numbers indicated above). All participants provided verbal and written informed consent before participation.

Orthostatic Stand Testing

The presence of OH was assessed using a standard active stand test. Using either a validated automated or manual cuff sphygmomanometer over the brachial artery, BP (in mm Hg) and HR (in bpm) were measured after 5 minutes of supine rest and then again after 1, 2, and 3 minutes of standing in a stationary position. OH was defined as a ≥20 mm Hg decrease in SBP and/or ≥10 mm Hg decrease in DBP sustained across 2 consecutive minutes of standing. In those with supine hypertension (sHTN, defined by consensus guidelines in those with nOH as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg),[e6] a secondary analysis was performed using a more stringent cutoff of ≥30 mm Hg decrease in SBP and/or a ≥15 mm Hg decrease in DBP, based on recent consensus guidelines.[e6]

The change in orthostatic BP was calculated as the difference between BP at supine baseline and after 3 minutes of standing (i.e., Δ = supine − standing). Similarly, orthostatic HR responses were calculated as the difference between HR at supine baseline and after 3 minutes of standing. The ΔHR/ΔSBP ratio was calculated by dividing the change in HR by the change in SBP at 3 minutes, as previously described.[15] OH with inadequate compensatory tachycardia ("OH-HR augmentation" group) was defined as a ΔHR/ΔSBP ratio <0.5 bpm/mm Hg[15] and used to approximate the frequency of nOH. All patients with OH on antihypertensives or other

Figure 3 SCOPA-AUT Total Score and Subscales



The overall SCOPA-AUT total score and each of 7 subscales were normalized to the total possible score and presented as a % impairment within each category (i.e., total score, gastrointestinal, bowel, urinary, cardiovascular, thermoregulatory, visual, and sexual function). SCOPA-AUT total score = 59, with subscales ranging from 1 to 5 questions (scores of 3–15). The open, light-shaded and heavy-shaded bars reflect the mean value for the normal BP group, OH, and OH-HR augmentation participants, respectively. *$p < 0.05$. BP = blood pressure; HR = heart rate; OH = orthostatic hypotension; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction.

medications known to cause OH were excluded from the final analysis.

Health History and Neurologic Battery

Participant health history and neurologic assessments have been previously described.[21] A detailed description of assessments is provided in the eMethods (links.lww.com/WNL/D221).

Statistical Analyses

Statistical analyses were run using SPSS and GraphPad Prism v8 and v9, with alpha set a priori at 0.05. Data are presented as mean with standard deviation or number and percentage of the whole. One-way analysis of variance with Tukey multiple comparison post hoc analyses or χ^2 analyses were computed when analyzing group differences between OH (including those meeting criteria for OH-HR augmentation) and normal BP participants (Figures 1–3; Tables 1–4) when appropriate based on numerical vs categorical data. The effect of sex was examined in participants with OH (eTable 1, links.lww.com/WNL/D221) using 2-tailed Student *t* tests comparing male vs female participants in OH and normal BP participants. The effect of antidepressant usage was analyzed in those with normal BP and OH, comparing participants reporting antidepressant usage with those not on antidepressants through 2-tailed Student *t* tests (eTable 2).

Data Availability

The full deidentified data set will be made accessible following standard written request.

Results

Of the 361 NAPS participant cohort, 340 with iRBD were included in the present analyses. The 21 excluded participants either were missing key variables (e.g., consecutive standing BP measurements; n = 13), or were taking exclusionary BP altering medications (in those with OH; n = 8). From these 340 participants, we identified OH in 93 (27%) participants. Of these, 72 (77%) met criteria for OH-HR augmentation, suggestive of nOH. The remaining 247 (73%) participants had normal orthostatic BP responses (normal BP group).

Demographics

The normal BP and OH groups were 63.4 ± 10.9 and 68.6 ± 6.7 years of age, respectively ($p < 0.0001$). There were no differences in race, ethnicity, or years of education between groups (Table 1). With respect to comorbidities, the only significant finding was a higher frequency of atrial fibrillation in the OH group compared with the normal BP group ($p = 0.0002$). Secondary analyses excluding the n = 6 OH participants with type II diabetes demonstrated no statistical differences in results, including all variables in Tables 1–4.

Table 1 Demographic and General/Mental Health Characteristics

	Normal BP (n = 247)	OH (n = 93)	OH-HR augmentation (n = 72)
Age, y	63.4 ± 10.9	68.6 ± 6.7[a]	69.0 ± 7.0[a]
Sex, male	84.1	81.7	83.3
Race and ethnicity			
Ethnicity, Hispanic/Latinx	2.8	94.6	2.8
Race, White	89.5	0.0	93.1
Race, Black or African American	2.8	0.0	0.0
Education			
Education, ≤12 y	14.6	19.35	20.83
Education, 13–14 y	15.0	12.9	12.5
Education, 15–18 y	50.6	49.5	47.2
Education, ≥19 y	19.4	17.2	18.1
General health			
Hypercholesterolemia	36.9	35.5	33.3
Arthritis	34.6	28.0	26.4
Thyroid disease	14.6	11.8	11.1
Type II diabetes	9.6	15.1	18.1
Cardiovascular and cerebrovascular			
Hypertension	36.8	37.6	43.1
Atrial fibrillation	4.5	24.7[a]	30.6[a]
Myocardial infarction	4.0	8.6	8.3
Stroke	2.8	2.2	2.8
Mental health			
BAI, score	8.3 ± 8.9	8.0 ± 8.9	7.9 ± 8.7
PHQ-9, score	5.5 ± 5.5	4.5 ± 4.9	4.6 ± 4.9
PCL-5, score	13.2 ± 16.6	10.1 ± 12.7	10.2 ± 12.7

Abbreviations: ANOVA = analysis of variance; BAI = Beck Anxiety Inventory; BP = blood pressure; OH = orthostatic hypotension; PCL-5 = Post-traumatic Stress Disorder Checklist for DSM-V; PHQ-9 = Patient Health Questionnaire-9.
Data presented as mean ± SD or % of total n.
Numerical data and categorical data were analyzed using 1-way ANOVA or χ^2, as appropriate.
[a] $p < 0.05$ vs the normal BP group.
[b] $p < 0.05$ vs OH.

No differences in Beck Anxiety Inventory, Post-traumatic Stress Disorder Checklist for DSM-V, or Patient Health Questionnaire-9 scores between groups were found (Table 1).

Active Stand Testing

As expected, BP regulation was impaired in the OH group. Supine SBP (Table 2; Figure 1) was higher in OH (151.1 ± 18.0 mm Hg, $p < 0.0001$) compared with the normal BP group (133.2 ± 16.4 mm Hg). The frequency of sHTN (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) was significantly higher in the OH group (72%) compared with the normal BP group (34%). Using a more stringent orthostatic BP drop of ≥30 mm Hg SBP or ≥15 mm Hg DBP in those with sHTN, 44/93 (47%) of our cohort still met criteria for OH.

After 3 minutes of standing, both SBP (122.9.5 ± 17.1 mm Hg, $p = 0.0008$) and DBP (77.6 ± 10.3 mm Hg, $p = 0.0073$) were lower in those with OH compared with the normal BP group (Table 2; Figure 1). This resulted in a ΔSBP and ΔDBP of −2.6 ± 9.3 mm Hg and 3.71 ± 7.4, respectively, in the normal BP group and a ΔSBP and ΔDBP of −28.2 ± 11.4 mm Hg and −7.27 ± 7.09, respectively, in the OH group (Table 2; Figure 2) The ΔHR/ΔSBP ratio was lower in the OH group compared with the normal BP group (0.4 ± 0.5 vs 2.1 ± 2.6;

Table 2 Hemodynamic and Autonomic Function Parameters

	Normal BP (n = 247)	OH (n = 93)	OH-HR augmentation (n = 72)
Supine SBP/DBP, mm Hg	133.2 ± 16.4/77.9 ± 9.4	151.1 ± 18.0[a]/84.9 ± 10.2[a]	151.5 ± 18.5[a]/84.9 ± 10.1[a]
Standing SBP/DBP, mm Hg	130.5 ± 19.1/81.6 ± 12.1	122.9 ± 17.1[a]/77.6 ± 10.3[a]	124.4 ± 17.5[a]/77.4 ± 10.2[a]
ΔSBP/ΔDBP, mm Hg	−2.6 ± 9.3/3.73 ± 7.4	−28.2 ± 11.4[a]/−7.3 ± 7.1[a]	−27.1 ± 12.3[a]/−7.6 ± 7.2[a]
Supine heart rate, bpm	64.0 ± 10.4	63.2 ± 11.2[a]	64.4 ± 11.4[a]
3-min standing heart rate, bpm	73.4 ± 13.8	72.0 ± 11.8	69.6 ± 10.4[a]
ΔHR, bpm	9.7 ± 8.4	8.7 ± 9.2	5.3 ± 6.5[a]
ΔHR/ΔSBP	2.1 ± 2.6	0.4 ± 0.5[a]	0.3 ± 0.5[a]
Supine hypertension	34.4	72.0	75.0
SCOPA-AUT, total raw	13.2 ± 7.7	14.3 ± 8.1	14.2 ± 8.0
SCOPA-AUT, total scaled	22.3 ± 12.9	24.3 ± 13.6	24 ± 13.5
Gastrointestinal, subscale	12.6 ± 14.1	13.7 ± 14.7	13.8 ± 14.5
Bowel, subscale	18.2 ± 17.9	22 ± 20.5	22.4 ± 20.9
Urinary, subscale	28.6 ± 17.8	30.4 ± 15.9	30.6 ± 16.4
Cardiovascular, subscale	8.8 ± 13.0	11.5 ± 15.3	10.8 ± 15.9
Thermoregulation, subscale	15.3 ± 16.1	12.4 ± 16.1	10.8 ± 15.3
Visual, subscale	17.8 ± 27.4	18.3 ± 26.7	18.1 ± 25
Sexual dysfunction, subscale	28.1 ± 32.0	36.2 ± 36.9	36.8 ± 38.4
Urinary incontinence, %	16.2	16.1	18.1[a,b]
Bowel incontinence, %	4.5	2.2	2.8

Abbreviations: ANOVA = analysis of variance; BP = blood pressure; DBP = diastolic blood pressure; HR = heart rate; OH = orthostatic hypotension; SBP = systolic blood pressure; SCOPA-AUT = Scales for Outcomes in Parkinson Disease-Autonomic Dysfunction (total score is raw/unscaled; subscale scores are normalized as a %impairment depending on each subscales possible score).
Data presented as mean ± SD or % of total n.
Numerical data and categorical data were analyzed using 1-way ANOVA or χ^2, as appropriate.
[a] $p < 0.05$ vs the normal BP group.
[b] $p < 0.05$ vs OH.

$p < 0.0001$) (Table 2; Figure 2). There was a significant correlation between supine SBP and ΔHR/ΔSBP ($r^2 = 0.14$; $p = 0.003$) such that 78% of those with OH could be correctly identified as having a ΔHR/ΔSBP <0.5 by a supine SBP of ≥130 mm Hg.

Autonomic Symptom Burden

Scales for Outcomes in PD-Autonomic Dysfunction (SCOPA-AUT) total autonomic symptom severity scores were no different between groups (Figure 3). Subscore analyses evaluating gastrointestinal, bowel, urinary, cardiovascular, thermoregulatory, and pupillomotor domains also showed no differences between groups.

Dream Enactment History

Detailed assessments of participants' RBD-related history were obtained (Table 3). The OH group reported an older age of dream enactment onset than those in the normal BP group (56.5 ± 18.6 vs 48.9 ± 18.2; $p = 0.0024$). No other differences with respect to dream-enacting behavior, history of self/bed partner injury, or association with medication usage were found. Similarly, the frequency of other sleep disorders, including sleep-disordered breathing, restless legs syndrome, insomnia, and periodic limb movement disorder, was similar across groups. Self-reported sleep quality through the SCOPA-Sleep and Epworth Sleepiness Scale was also similar across groups.

Cognitive, Motor, and Sensory Function

Detailed assessments of cognitive, motor, and sensory function were obtained. For the Phenomic/Category Fluency Animal category, the OH group had lower scores (18.9 ± 5.3, $p = 0079$) compared with the normal BP group (20.9 ± 5.5). The OH group showed lower scores for the Purdue Pegboard test (10.8 ± 2.3 vs 10.9 ± 2.5, $p < 0.0001$) and Alternative Tap Test (175.1 ± 41.1 vs 176.2 ± 38.7, $p < 0.0001$) compared with the normal BP group, although the clinical relevance for this is likely minimal. The only other significant difference was olfactory function (Brief Smell Identification Test [BSIT])

Table 3 RBD Behavior and Sleep Disorders Across Groups

	Normal BP (n = 247)	OH (n = 93)	OH-HR augmentation (n = 72)
RBD behavior and characteristics			
Age of RBD onset, y	48.9 ± 18.2	56.5 ± 18.6[a]	56.8 ± 18.9[a]
Movement/talking	97.6	98.9	100.0
Movement/talking with dreams, always	58.3	38.1	59.7
RBD behavior: injured self, ever	54.7	55.9	58.3
RBD behavior: injured bed partner, ever	42.5	32.3	34.7
Other sleep disorders			
Obstructive sleep apnea	56.3	49.5	52.8
Restless leg syndrome	17.8	15.1	12.5
Insomnia	30.0	22.6	23.6
Periodic limb movement	15.4	17.2	16.7
Sleep questionnaires			
SCOPA-Sleep (participant), score	12.0 ± 6.7	10.7 ± 6.4	10.8 ± 6.8
SCOPA-Sleep (coparticipant), score	12.9 ± 7.4	11.7 ± 6.8	12.2 ± 7.2
Epworth Sleepiness Scale, score	6.8 ± 4.9	5.8 ± 4.4	6.2 ± 4.7

Abbreviations: ANOVA = analysis of variance; BP = blood pressure; OH = orthostatic hypotension; RBD = REM sleep behavior disorder.
Data presented as mean ± SD or % of total n.
Numerical data and categorical data were analyzed using 1-way ANOVA or χ^2, as appropriate.
[a] $p < 0.05$ vs the normal BP group.
[b] $p < 0.05$ vs OH.

where the OH group had lower scores (6.1 ± 2.7 vs 7.7 ± 3.0, $p < 0.0001$) compared with the normal BP group (Table 4).

Predictors of OH

To explore correlations between OH and other prodromal features common in iRBD, multiple linear regression (MLR) analyses were computed for 3 separate outcome variables (ΔSBP, ΔDBP, and ΔHR/ΔSBP). Predictor variables were chosen a priori and based on expert opinion, consisting of age, Farnsworth Munsell 100 Color Hue test (FM-100), BSIT, Montreal Cognitive Assessment (MoCA), and Movement Disorders Society-sponsored revision of the Unified PD Rating Scale part III, and all predictor variables passed the collinearity threshold (variance inflation index <3.0 corresponding to an R^2 of <0.7). These MLR models predicting ΔSBP, ΔDBP, and ΔHR/ΔSBP for the OH group demonstrated that the only effect observed was age, for which an older age predicted ΔDBP ($p = 0.0182$, $t = 2.437$, $\beta = -0.42$).

Given the known association between male sex and RBD, the effect of sex within OH and normal BP groups was assessed as an exploratory outcome (eTable 1, links.lww.com/WNL/D221). We found 76 (82%) male participants in the OH group and 201 (81%) male participants in the normal BP groups, compared with 17 (18%) female participants in the OH group and 46 (19%) female participants in the normal BP group. Age was no different between groups. Male participants with OH reported worse olfaction (BSIT; $p = 0.0393$) than female participants with OH. Male participants in the normal BP group reported worse color vision (FM-100; $p = 0.0168$), worse olfaction (BSIT; $p = 0.0350$), and worse cognition (MoCA; $p = 0.0035$) than female participants in the normal BP group.

Antidepressant Usage

To address the potential effects of antidepressant use on active stand test results and autonomic symptom burden, we performed a subanalysis of those iRBD patients with OH taking antidepressant medications (eTable 2, links.lww.com/WNL/D221). These patients had a slightly older age of RBD symptom onset (53.3 ± 15.9 vs 59.5 ± 11.1, respectively, $p = 0.0377$) and slightly higher cardiovascular SCOPA-AUT symptom scores (15.5 ± 18.7 vs 7.2 ± 9.2, respectively, $p = 0.0088$). The remainder of pertinent demographic and autonomic variables, including age, severity of injurious RBD behaviors, severity of OH, and severity of autonomic symptoms, as measured by the remainder of the SCOPA-AUT subscales and total scores, were no different between groups.

OH-HR Augmentation Subanalysis

The OH-HR augmentation group was older (69.0 ± 7.0) than the normal BP group (63.4 ± 10.9; $p < 0.0001$) and reported an older age of RBD onset (56.8 ± 18.9) than those in the normal BP group (48.9 ± 18.2; $p = 0.0049$). With respect to

Table 4 Cognitive, Motor, and Sensory Function Across Groups

	Normal BP (n = 247)	OH (n = 93)	OH-HR augmentation (n = 72)
Cognitive function			
Montreal Cognitive Assessment	26.3 ± 5.3	26.3 ± 5.5	26.4 ± 6.0
Craft story			
Immediate verbatim	13.1 ± 5.3	13.0 ± 5.1	13.5 ± 4.9
Delay verbatim	15.5 ± 6.8	14.6 ± 6.6	15.1 ± 6.4
Benson			
Immediate	15.6 ± 2.0	15.3 ± 2.6	15.3 ± 2.9
Delay	11.3 ± 3.6	10.8 ± 3.4	10.9 ± 3.3
Number span			
Total forward	8.4 ± 2.4	8.0 ± 2.2	7.9 ± 2.2
Total backward	6.8 ± 2.3	6.6 ± 2.1	6.7 ± 2.3
Trails A, s	39.2 ± 63.3	47.6 ± 101.5	50.6 ± 115.0
Trails B, s	104.1 ± 127.7	103.1 ± 105.2	105.1 ± 114.7
Multilingual Naming Test	30.2 ± 2.0	29.8 ± 3.8	29.8 ± 4.2
Phonemic/categorical fluency			
F words	13.8 ± 5.3	14.1 ± 5.2	13.8 ± 5.3
L words	12.8 ± 5.3	12.8 ± 5.1	12.6 ± 5.3
Animals	20.9 ± 5.5	18.9 ± 5.3[a]	18.9 ± 5.4[a]
Vegetables	13.9 ± 4.0	14.2 ± 4.7	14.5 ± 4.9
Motor			
MDS-UPDRS part 3, score	2.0 ± 3.3	2.1 ± 3.9	2.4 ± 4.4
Purdue Pegboard, dominant hand	10.9 ± 2.5	10.8 ± 2.3	10.8 ± 2.4[a]
Alternate Tap Test, dominant hand	176.2 ± 38.7	175.1 ± 41.1[a]	178.8 ± 40.0[a]
Timed Up and Go, s	9.0 ± 3.5	8.7 ± 3.3	8.6 ± 3.5
Sensory function			
Farnsworth-Munsell Color Vision Test	141.4 ± 102.0	152.1 ± 96.8	146.0 ± 94.8
Brief Smell Identification Test	7.7 ± 3.0	6.1 ± 2.7[a]	6.0 ± 2.8[a]

Abbreviations: ANOVA = analysis of variance; BP = blood pressure; MDS-UPDRS = Movement Disorders Society-sponsored revision of Unified Parkinson Disease Rating Scale; OH = orthostatic hypotension.
Data presented as mean ± SD or % of total n.
Numerical data and categorical data were analyzed using 1-way ANOVA or χ^2, as appropriate.
[a] $p < 0.05$ vs normal BP.
[b] $p < 0.05$ vs OH.

comorbidities, the frequency of atrial fibrillation was higher in the OH-HR augmentation group compared with the normal BP group ($p < 0.0001$). As expected, BP and HR regulation was impaired in the OH-HR augmentation group and similar to the results found in our primary analyses comparing OH and normal BP groups (Table 2; Figure 1), with the exception of ΔHR/ΔSBP ratio, which by definition was lower in the OH-HR augmentation group (0.3 ± 0.5) compared with the normal BP group (2.1 ± 2.6; $p < 0.0001$). Cognitive and olfactory abnormalities were also similar to the results found in our primary analyses comparing OH and normal BP groups (Table 4).

Discussion

We report the frequency of OH in the largest cohort of patients with iRBD to prospectively assess orthostatic BP and

HR data, finding that OH was common, with 26% of patients meeting criteria for this diagnosis, most of whom (21%) also met criteria for OH-HR augmentation, suggestive of nOH. We also found that 72% of patients with OH had sHTN, with 15% of this group meeting criteria for OH when following the more stringent orthostatic BP cutoff of ≥30/15 mm Hg for SBP/DBP, respectively. This frequency is substantially higher than most population-based estimates of OH and nOH. A meta-analysis of OH in the elderly reported a prevalence of 18.4%, based on a pooled analysis of high-quality studies; however, significant variability in prevalence estimates was noted, and sHTN was not accounted for.[22] When excluding those on medications known to cause OH, as we did in our study, prevalence rates as low as 6.4% were reported.[23] Although the rates of nOH are not available, it is believed to be a relatively rare condition, affecting <200,000 individuals in the United States.[24] Thus, our findings suggesting nOH in approximately 1 of 5 participants with iRBD are much higher than population-based estimates, especially when considering the estimated iRBD prevalence of 1%.[25-27]

The recognition of OH is especially important given the morbidity and mortality associated with this condition. OH is a common cause for hospitalization, with an estimated hospitalization rate of 36 per 100,000 adults.[28] Increasing age confers greater risk, with an estimated hospitalization rate of 233 per 100,000 in those older than 75 years, with a median length of stay of 3 days and an overall in-hospital mortality rate of 0.9%.[28] OH increases the risk of syncope and falls, with greater risk of head trauma and large bone fractures.[29]

Despite the high frequency of OH in our cohort of participants with iRBD, autonomic symptom burden, as measured by total and subdomain SCOPA-AUT scores, was no different from scores in participants without OH, suggestive of impaired autonomic symptom recognition. Other groups have also demonstrated that orthostatic intolerance is impaired in those with OH and nOH. In one study of 210 patients with PD and nOH, only 16% of patients reported symptoms that corresponded with their drop in BP.[30] In another study of 89 patients with OH (% nOH not specified), including 41 patients with synucleinopathies, 24% reported mild symptoms of orthostatic intolerance and 43% reported no symptoms at all, despite significant drops in BP.[31] The authors hypothesized that attenuation of the subjective response to hypotension may be secondary to the degeneration of those structures responsible for sensing impaired cerebral perfusion or alternatively could represent attenuation of interoception due to the neurodegenerative process, a form of anosognosia. To test this hypothesis, one study[32] compared orthostatic symptoms experienced during head-up tilt testing in those with MSA, a primarily preganglionic disorder, to those with peripheral autonomic neuropathy, a primarily postganglionic disorder. The authors found no difference between groups, suggesting that lack of symptom awareness in those with nOH may be more likely due to cerebral hypoperfusion than degeneration of central afferent systems. Our findings in iRBD, a disorder localized to preganglionic REM control centers in the dorsal pons, supports this theory.

Longitudinal studies in iRBD have demonstrated that those with higher total SCOPA-AUT scores have a greater risk of phenoconversion to a defined synucleinopathy. In one study,[8] the domain associated with the greatest risk of phenoconversion was the cardiovascular domain (adjusted odds ratio 1.28, 95% CI 1.010–1.6), which includes those symptoms most commonly reported by individuals with nOH. In another study,[33] the autonomic symptoms of constipation (HR 1.67 [1.2–2.2]) and urinary dysfunction (HR 1.06 [0.7–1.5]) were associated with greater phenoconversion risk (cardiovascular symptoms were not consistently reported in this study). Orthostatic stand testing was performed in this study, however not standardized (standing BPs at 1 and 3 minutes were alternatively reported); heart rate was not reported, and OH was defined as a SBP drop of >10 mm Hg, and the presence of a SBP drop resulted in a hazard ratio of 1.37 (0.9–2.1).[33] A total of 352 patients in this study (28%) phenoconverted to a defined synucleinopathy, with a mean interval between baseline evaluation and phenoconversion of 4.6 ± 3.5 years.

nOH, like iRBD, can be a prodromal feature of underlying synuclein-driven neurodegenerative disease. In cases where the OH presents with gastrointestinal, genitourinary, and sudomotor abnormalities, patients can be given the diagnosis of pure autonomic failure (PAF). Neuropathologic studies of PAF have demonstrated deposition of pathologic alpha-synuclein in peripheral autonomic neurons within sympathetic ganglia as well as Lewy neurites throughout autonomic axons of the heart, periadrenal tissue, bladder, skin, and colon,[34] supporting the concept of PAF as a synucleinopathy subtype. Furthermore, longitudinal studies have demonstrated that a substantial proportion of those with PAF will eventually phenoconvert to PD, DLB, or MSA, establishing PAF as another prodromal synuclein disease state in a subset of patients, such as iRBD. In one longitudinal study of 74 individuals with PAF (70% male) presenting with nOH and followed prospectively for 4 years, 25 patients (35%) developed DLB, 6 patients (8%) developed PD, and 6 patients (8%) developed MSA, with a cumulative incidence of phenoconversion of 34%.[35] Patients who developed MSA had a younger age of nOH onset (median 53, interquartile range [IQR] 8 years), more severe bladder/bowel dysfunction, normal olfaction, and a more robust HR response in the setting of OH on head-up tilt, indicating less impaired postganglionic cardiac chronotropic responses; however, mean ΔHR/ΔSBP ratios were still in the abnormal range, and there was significant variability in HR responses. Those who developed PD and DLB had an older age of nOH onset (PD, median 60 [IQR 9] years; DLB, median 66 [IQR 7] years), abnormal olfaction, and a more severely blunted HR response in the setting of OH on head-up tilt, indicating abnormal postganglionic cardiac chronotropic responses. Probable RBD, as assessed by a positive response to the RBD single

item screen,[36] was present in 74% of patients at study entry, and the presence of probable RBD was associated with a greater risk of phenoconversion to a defined synucleinopathy (odds ratio 7.1, 95% CI 1.5–33.5). Considering these studies in the iRBD and PAF populations, longitudinal follow-up of patients with iRBD in our NAPS cohort will be critical to further evaluate the role of autonomic cardiovascular dysfunction, including OH and nOH, as a biomarker of disease progression in iRBD, as well as future synucleinopathy subtype. Future studies should also focus on the distinction between patients with iRBD + OH, with or without HR augmentation, and whether PAF + RBD and iRBD + OH represent similar phenotypic expressions of synuclein-driven neurodegeneration.

sHTN was also common in our cohort, affecting 72% of those with OH. iRBD patients with sHTN had a greater fall in SBP compared with those who were normotensive, indicating more severe baroreflex impairment. sHTN is common in nOH and is estimated to affect approximately 50% of patients with this condition.[37] Although no studies have systematically evaluated the complication rates of sHTN, this condition can potentially result in complications of hypertensive emergencies (e.g., cerebral hemorrhage, ischemic stroke, pulmonary edema, myocardial infarction) and may also result in greater risk of left ventricular hypertrophy and renal impairment, as has been demonstrated in diabetics with autonomic cardiovascular impairment.[38] In addition, sHTN can induce nocturnal diuresis and natriuresis, leading to more severe OH in the morning and a greater risk of falls. We also found that patients with OH in our cohort had much higher rates of atrial fibrillation. This association has been noted in other cohorts,[39] suggesting shared pathophysiologic mechanisms of autonomic dysfunction. In support of this possibility, other studies have demonstrated impaired baroreflex gain in those with atrial fibrillation.[40] Clinicians should be aware of this association when interpreting the electrocardiogram on overnight vPSGs in those with iRBD, especially if comorbid OH has been identified.

Limitations of our study include the fact that patients in the normal BP group on antihypertensives and other medications known to cause OH were not excluded from the analysis. However, we felt this appropriate to maintain an adequate sample size and to maintain an appropriate comparison group. However, this may have influenced our sHTN comparisons, in that sHTN may have been masked by antihypertensive use in some patients in the normal BP group. However, as sHTN is strongly correlated with nOH and baroreflex impairment, we do not believe antihypertensive use significantly affected this analysis, as most iRBD patients with sHTN likely have autonomic impairment due to the neurodegenerative process. Another class of medications that might have affected our results is selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs), which may increase BP and HR and are commonly prescribed to patients with iRBD. By including participants on these medications, it is possible that we might be underreporting the true frequency of nOH in iRBD, as 32% of the OH group and 47% of the normal BP group were taking SSRIs/SNRIs, some of which may have resulted in higher BPs and therefore masked OH in some patients. However, a subanalysis of OH patients within our cohort on antidepressant medications revealed minimal differences when compared with those patients with OH not on antidepressants.

In addition, we included 6 participants who reported a diagnosis of type II diabetes mellitus in our OH group; however, a secondary analysis after excluding these participants demonstrated no statistical differences in our findings. Although the NAPS protocol does query for participants to self-report comorbid conditions that might affect autonomic function, it does not verify these diagnoses or include systematic laboratory measures to exclude these conditions definitively (e.g., B12, hemoglobin A1c, serum-free light chains); thus, it is possible that some causes of secondary nOH were not captured in some patients. In addition, our protocol captured BP and HR measurements within 3 minutes of standing only and may have missed some patients with delayed OH, defined as OH occurring after the upright 3-minute mark, a condition that has been also associated with synucleinopathies.[41] The high percentage of those with atrial fibrillation may have also contributed to inaccuracies of single HR measurements, as ECG was not performed during stand testing. While the ΔHR/ΔSBP is a surrogate marker of nOH, cardiovascular autonomic reflex testing (ART) remains the gold standard for diagnosing this condition. Although ART was not performed in the NAPS baseline cohort, we performed ART on a prior cohort of iRBD participants,[42] finding nOH in 7/25 (28%) on HUTT, with 5 patients exhibiting classic nOH and 2 delayed nOH. The phase IV overshoot of the Valsalva maneuver, another measure of sympathetic adrenergic function important in confirming nOH, was reduced in 11/25 (44%) of our cohort. In another study of 18 patients with vPSG-proven iRBD, 13 patients had symptoms of orthostatic intolerance, asymptomatic OH, or syncope, and abnormal autonomic function testing was found in 15 (83%) patients with iRBD, including 11 (61%) with adrenegic impairments.[43] Interestingly, greater autonomic dysfunction was more associated with eventual DLB than PD disease trajectory, suggesting autonomic function could be a valuable phenotyping marker. Further longitudinal studies of autonomic function in iRBD will be necessary to fully characterize autonomic dysfunction in iRBD and determine its relationships with disease trajectory and conversion risk. It should also be noted that iRBD patients with isolated preganglionic autonomic degeneration, as seen in MSA, may manifest a normal compensatory tachycardia with pathologic orthostatic BP falls, thus resulting in a normal ΔHR/ΔSBP ratio. Recognizing that this ratio is not perfect for classifying nOH vs non-nOH, we aim to incorporate ART in a subset of patients with iRBD in NAPS stage 2 to provide more detailed measures of autonomic cardiovascular function and to validate our findings. It would also be informative to incorporate time and frequency domain analyses of HR variability on both active stand testing or

HUTT and overnight vPSG as additional measures of autonomic function. NAPS stage 2 will also include a group of age-adjusted control patients without iRBD. Lack of this comparison group is another limitation of this preliminary study, as other conditions can result in OH. We hope to include this additional comparison group in future analyses. Finally, our cohort comprised of only individuals in the United States and Canada, and most of our patients identified as Caucasian; thus, our cohort may not be generalizable to a more diverse sample of the global iRBD population. Despite these limitations, our harmonized multicenter cohort represents the largest group of patients with iRBD to undergo standardized measures of orthostatic BP and HR analyses.

In conclusion, our findings suggest that OH is common in iRBD, affecting nearly 1 in 4 patients, with sHTN existing in 3 of 4 of those with OH. Despite this, symptom recognition of autonomic impairment was generally impaired. Given the morbidity and mortality associated with OH in general and nOH in particular, clinicians evaluating patients with RBD should be aware of this association. Patients should be assessed for symptoms of orthostatic intolerance and queried for recent falls, and orthostatic BP measurements should be routinely performed in the evaluation of all patients with RBD.

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Continued

Appendix 1 *(continued)*

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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/D242.

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