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Blunted tachycardia and cardiac sympathetic denervation in isolated rapid eye movement sleep behavior disorder

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Abstract

Background Isolated rapid eye movement sleep behavior disorder (iRBD) serves as a prodromal phase of Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Blunted tachycardia (BT) during postural changes indicates neurogenic orthostatic hypotension, a marker of autonomic dysfunction. We aimed to investigate whether BT is associated with cardiac sympathetic neurogenic denervation. Additionally, we conducted a preliminary short-term follow-up to examine the potential prognostic significance of BT regarding phenoconversion and mortality.

Methods Forty-three patients with iRBD at Shiga University of Medical Science Hospital underwent active standing tests to identify BT, defined by a specific ratio of decrease in systolic blood pressure to inadequate increase in heart rate after standing, and orthostatic hypotension. ^{123}I-metaiodobenzylguanidine myocardial scintigraphy (^{123}I-MIBG) and dopamine transporter single-photon emission computed tomography (DAT-SPECT) were performed. Participants were followed up for 3.4 ± 2.4 years for phenoconversion and 4.0 ± 2.3 years for mortality assessment, and the risk of events was analyzed using log-rank tests.

Results Among the 43 participants (mean age, 72.3 ± 7.9 years; 8 female), 17 met the BT criteria. We found no significant comorbidity-related differences in hypertension or diabetes between the BT(+) and BT(-) groups. Orthostatic hypotension was more prevalent in the BT(+) group than in the BT(-) group (47.1% vs 7.7%, $p = 0.003$). BT(+) patients were older with a lower early and delayed MIBG uptake; however, no significant differences were observed in DAT accumulation. Phenoconversion was observed in seven (41.2%) BT(+) and seven (26.9%) BT(-) patients. Three deaths were recorded in the BT(+) group (17.6%) and three in the BT(-) group (11.5%). No significant differences were observed in the risk of phenoconversion or mortality between the groups.

Conclusions We have identified the possibility that BT reflects cardiac sympathetic neurogenic denervation in patients with iRBD. Future research is needed to elucidate the potential prognostic value of BT.

Keywords Autonomic dysfunction, Blunted tachycardia, Longitudinal study, Orthostatic hypotension, Phenoconversion, Rapid eye movement sleep behavior disorder

Background

Rapid eye movement (REM) sleep behavior disorder (RBD) is a type of REM parasomnia characterized by dream-enacting behaviors [1, 2]. Approximately 1% of middle-aged and older adults have RBD, confirmed by polysomnography [3, 4]. RBD has been considered a prodromal phase and an early manifestation of various

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neurodegenerative diseases, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA) [2, 5]. RBD that occurs independently and has not yet progressed to PD, DLB, or MSA and is not associated with other causative conditions, such as tumors, brainstem strokes, or autoimmune diseases, is termed isolated RBD (iRBD) [6]. Notably, a significant proportion of patients with iRBD eventually develop neurodegenerative diseases, such as PD or DLB (82.4% at 10.5 years of follow-up) [7]. In iRBD, various symptoms and abnormalities emerge, similar to those in PD or DLB, including autonomic nervous system dysfunctions, such as orthostatic hypotension (OH) [8], constipation, and urinary symptoms [9]; minor cognitive impairments [10]; psychiatric symptoms, such as minor hallucinations [11] and depression [12]; and abnormal findings in cardiac sympathetic innervation assessed using ^{123}I-metaiodobenzylguanidine myocardial scintigraphy (^{123}I-MIBG) and dopamine transporter (DAT) single-photon emission computed tomography (DAT-SPECT) [13–16].

OH is a persistent, consistent, orthostatic decrease in blood pressure (BP) 3 min after standing, with a decrease in systolic BP (sBP) of 20 mmHg or diastolic BP (dBP) of 10 mmHg [17]. It affects one- to two-thirds of older adults [18–20] and can manifest asymptomatically or with symptoms such as lightheadedness or syncope [21]. Various factors contribute to OH, including drug-induced effects (e.g., those of vasodilators, diuretics, and tricyclic antidepressants), secondary non-neurogenic causes (e.g., hypovolemia and cardiac pump failure), secondary neurogenic causes (e.g., peripheral neuropathies due to diabetes mellitus and spinal cord problems), and primary neurogenic causes [21]. Cases of neurogenic OH (nOH) can be further classified into two categories: those with sympathetic neurogenic denervation (e.g., PD, DLB, and pure autonomic failure) and those with intact sympathetic neurogenic innervation (e.g., MSA and autoimmune ganglionopathy). ^{123}I-MIBG imaging can help identify cardiac sympathetic neurogenic denervation [22, 23]. When OH complicates neurodegenerative diseases, such as PD and DLB, they are associated with poor prognoses, including increased mortality, falls, trauma-related falls, and cognitive decline [24–27]. Given that neurodegenerative diseases predominantly affect older adults and OH are commonly observed in older individuals, it is important to differentiate between OH and nOH. Although diagnosing nOH involves abnormalities in beat-to-beat BP variability during the Valsalva maneuver [28] and poor plasma norepinephrine response to orthostasis [29], these tests can be burdensome for patients and healthcare providers in routine clinical practice.

Recently, blunted tachycardia (BT) during postural change has gained attention as an indicator of nOH in patients with neurodegenerative diseases [30]. BT, defined as a decrease in the heart rate (HR) relative to sBP change (ΔHR/ΔsBP) of < 0.5 bpm/mmHg after postural change on a tilt table, has been reported to distinguish nOH from non-neurogenic OH with a sensitivity of 91% and specificity of 88% [30]. The use of HR and sBP observations during postural changes for detecting nOH is easily applicable in routine clinical settings. A recent report indicated that BT in patients with pure autonomic failure is a risk factor for future phenoconversion to PD [31]. Thus, BT could be a specific marker of neurodegenerative diseases and may indicate prognosis.

However, the clinical significance of BT in iRBD remains elusive, particularly considering its role as an indicator of nOH. A recent cross-sectional study revealed a notable prevalence of OH in approximately 27% of the patients with iRBD, and 77% of those with OH exhibited an impaired HR response, indicative of BT [32]. However, the previous study is limited by their cross-sectional design and the absence of nuclear medicine assessments, underscoring a critical gap in our understanding of the significance of BT predictive in iRBD. ^{123}I-MIBG distinguishes iRBD and Lewy body diseases from other neurological disorders, such as corticobasal degeneration and progressive supranuclear palsy, as well as healthy individuals [16, 33, 34]. A recent nuclear imaging study has shown that PD subtypes with reduced ^{123}I-MIBG uptake in the early stages of the disease have a poor prognosis [35]. DAT-SPECT robustly predicts future phenoconversion in iRBD [10, 13, 36–38]. To establish a strong connection between the cardiovascular pathology of BT and neurodegeneration, nuclear medicine examinations are crucial. Moreover, longitudinal outcomes in patients with iRBD are important, especially given their pre-phenoconversion status, for informing prognosis, including phenoconversion and mortality, essential for both patients, their families, and researchers focused on disease-modifying trials [39].

We recommend using BT as an early assessment tool for autonomic dysfunction in patients with iRBD. Focusing on nOH often involves consideration of the influences of cardiovascular diseases and medications. Furthermore, autonomic dysfunctions are less pronounced in iRBD compared with in PD and DLB, suggesting that BT might be more commonly applicable than nOH. The pathological significance of BT in individuals without OH remains unclear. However, focusing on BT regardless of the presence of OH in iRBD patients may elucidate its pathological significance.

Therefore, in this study, we aimed to bridge this gap by leveraging nuclear medicine tests, such as ^{123}I-MIBG and DAT-SPECT. Additionally, we conducted a short-term preliminary follow-up investigation. By elucidating the

relationship between BT, nuclear medicine findings, and long-term outcomes, including phenoconversion, death, and trauma-related falls, we aimed to investigate the pathological significance of BT and its prognostic potential in iRBD.

Methods

Patient selection

This retrospective cohort study was conducted between the comprehensive clinical assessment (baseline evaluation) and censoring date to investigate whether the events (of phenoconversion, death, or fractures due to falls) occurred.

The inclusion criteria were as follows: patients who met the diagnostic criteria for RBD based on the International Classification of Sleep Disorders, third edition [1], confirmed by polysomnography, and those with medical records of iRBD (without a diagnosis of PD [40], DLB [41], MSA [42], or dementia according to the Diagnostic and Statistical Manual of Mental Disorders-5 [43]) who visited the Shiga University of Medical Science Hospital between June 1, 2016, and July 31, 2023. The exclusion criteria were as follows: those who took antidepressants or antiparkinsonian agents, had severe sleep apnea (apnea–hypopnea index of 30) [44], schizophrenia spectrum disorders or other psychotic disorders (Diagnostic and Statistical Manual of Mental Disorders-5) [43], and with RBD secondary to stroke.

The patients underwent baseline evaluation between June 1, 2016, and July 31, 2023, including the active standing test (described below), with censoring on February 5, 2024. During the baseline evaluation, we excluded patients for whom data measurements failed during the active standing test. In addition, patients who did not undergo DAT-SPECT using [^{123}I] N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane were excluded because DAT-SPECT findings serve as a valuable marker for phenoconversion and provide a reference of neurodegeneration [10, 13, 36–38].

We did not calculate the required sample size due to the exploratory nature of the study. This study was approved by the Research Ethics Committee of Shiga University of Medical Science (R2017-199). This study was part of the investigation into risk factors for phenoconversion and had been approved by the committee (R2017-160). Written informed consent to participate was obtained from all patients.

Baseline evaluation

Demographic data

Demographic data collected at baseline included age, sex, years of education, disease duration since RBD occurrence (the first time the symptoms of RBD were observed, as confirmed by the family members), and age at onset of RBD. Alcohol consumption, smoking habits, comorbidities (arterial hypertension, coronary artery disease, myocardial infarction, diabetes mellitus, arrhythmia, atrial fibrillation, hypercholesterolemia, thyroid disease, and stroke), and medications (calcium-channel blockers, angiotensin-converting enzyme and angiotensin II type inhibitors, beta-blockers, organic nitrates, antipsychotics, melatonin, clonazepam, and pramipexole) were also assessed because these factors would affect BP dynamics and autonomic nervous system function [45]. We interviewed first-degree relatives of patients with a family history of PD or dementia.

Active standing test

Procedures of active standing test and HRV measurement We conducted the active standing test, also known as the orthostatic challenge test, and divided patients into two groups, BT (+) or BT(-). The test consists of two phases: supine and standing positions. Detailed information regarding the procedure has been previously reported [8]. We conducted the active standing test following a standardized protocol, carefully designed to control for variables such as alcohol, tobacco, and caffeine consumption; the timing of the last meal before the test; and room temperature. These controls are crucial because various factors, including diet and ambient temperature, can influence the autonomic functions associated with regulating BP and HR [46–48].

Before the test, the patients were equipped with a wearable sensor to detect the R-R interval (RRI) of an electrocardiogram [49] and a sphygmomanometer. They were instructed to lie on a bed approximately 40 cm above the floor without talking and sleeping during the tests. After confirming the operation of the measuring devices in the supine position (>2 min), the patients' BP (sBP and dBP) and HR were measured. In the supine position, BP and HR were measured five times at 3-min intervals. After 15 min in the supine position, the patients were asked to stand for 15 min. BP and HR were measured in the standing position 15 times at 1-min intervals. The examiner carefully observed each patient. After the active standing test, the examiner asked the patients confirmed the presence or absence of symptoms, such as dizziness, titubation, blurry vision, syncope, or nausea.

RRI, which represents the interval between consecutive R-waves on an electrocardiogram, characterizes the biological phenomenon known as HRV [50]. The quantitative assessment of HRV involves HRV indices comprising time-domain indices and Poincaré plots [50]. The filtering

and analysis processes of RRI have been described in a previous report [8]. Six HRV indices in the 5 min preceding standing were calculated, including the standard deviation of all RRIs, root mean square of successive differences, percentage of adjacent intervals that varied by > 50 ms, standard deviation of the Poincaré plot along its minor axis (SD1), standard deviation of the Poincaré plot along its major axis (SD2), and ratio of SD1 to SD2 on the Poincaré plot (SD1/SD2). Although frequency-domain analysis is commonly used for HRV assessment, short-term frequency-domain analysis is vulnerable to arrhythmias. Given the prevalence of premature atrial contractions or premature ventricular contractions among older adults [51, 52], frequency-domain analysis is not considered appropriate and was not employed as an input feature for this demographic.

BT and OH definition and grouping Based on the outcomes of the active standing test, BT and OH were defined as follows. The mean values of the supine BP and HR for each participant were defined as supine BP and HR, respectively.

Criteria for BT Based on previous research [30], patients were defined as BT(+) if they satisfied the following two criteria: (i) sBP at 3 min after standing was lower than supine sBP and (ii) the ratio of the increase in the HR (ΔHR) to the decrease in the sBP (ΔsBP) (ΔHR/ΔsBP) at 3 min after standing was < 0.5 bpm/mmHg. Those who did not meet either criterion (i) or (ii) were defined as BT(-). Patients with ΔsBP of ≤ 0, that is, those with standing sBP equal to or greater than supine sBP, were not included in the calculation of ΔHR/ΔsBP because these patients did not satisfy criterion (i).

Criteria for OH Based on previous studies, OH was defined as follows [19, 53–55]: (i) decrease in sBP by ≥ 20 mmHg or dBP by ≥ 10 mmHg compared with supine BP at 1 or 3 min after standing; and (ii) decrease in sBP to ≤ 90 mmHg. For patients with a supine sBP of ≥ 160 mmHg, a decrease in sBP of ≥ 30 mmHg and/or decrease in dBP of ≥ 15 mmHg was defined as OH (+) instead of an sBP of ≥ 20 mmHg or a dBP of ≥ 10 mmHg [20].

Clinical investigation

Autonomic nervous system examination The Scale for Outcomes in PD-Autonomic (SCOPA-AUT), a validated scale for autonomic dysfunction in patients with PD, was used to assess autonomic dysfunction [56]. Twenty-five items (0–3 points per item) were included in the SCOPA-AUT, which evaluated the following domains: gastrointestinal (7 items), urinary (6 items), cardiovascular (3 items), thermoregulatory (4 items), pupillomotor (1 item), and sexual dysfunction domains (two items for male individuals and two for female individuals), as well as a total score (23).

Nuclear medicine examination As part of our study on risk factors for phenoconversion, all patients underwent nuclear medicine imaging, specifically DAT-SPECT. However, the decision to perform ^{123}I-MIBG imaging was left to the discretion of the patients, given the substantial financial burden associated with the procedure.

To assess the extent of dopaminergic neuronal degeneration, DAT-SPECT was performed. We calculated the specific-to-non-displaceable binding ratios in the right and left striata, as well as the average value.

^{123}I-MIBG scintigraphy was performed using a dual-head camera equipped with an extended low-energy general-purpose ELEGP collimator (GE Healthcare, Chicago, IL, USA). Data were collected at 15-min (early) and 3-h time (delayed) points after the injection of 111 MBq of ^{123}I-MIBG. A static image was obtained using a 256 × 256 matrix. The regions of interest surrounding the heart and mediastinum were drawn manually. To calculate the heart-to-mediastinum (H/M) ratio, tracer uptake was measured within each region of interest. Following previous studies on neurodegenerative disorders, we defined an early H/M ratio of < 2.28 [57] and a delayed H/M ratio of < 1.78 [58, 59] as abnormal. The washout rate was calculated as follows:

$$\text{washout ratio} = \left(\left(\text{early H/M mean} - \text{delayed H/M mean}\right) / \text{early H /M mean}\right) \times 100$$

Cognitive function The following examinations were used to assess patients' cognitive functions:

a) Mini-Mental State Examination (MMSE): A screening examination for dementia with a cut-off score of < 24 (maximum score of 30) [60].
b) Frontal Assessment Battery (FAB): An assessment of frontal lobe functioning with a cut-off score of < 12 (maximum of 18) [61, 62].
c) Montréal Cognitive Assessment: A screening test designed to detect mild cognitive impairment with a cut-off score of < 23 (maximum score of 30) [63, 64].

Psychiatric symptoms Minor hallucinations, common psychotic symptoms of iRBD, include visual illusions, presence hallucinations, and passage hallucinations [11]. A trained physician (YS and HK) conducted semi-structured interviews to assess minor hallucinations [11]. In addition, we conducted a noise pareidolia test. We measured pareidolic responses to 32 images without a face (maximum score 32) [65], and the cut-off score was set as ≥ 2 [66].

We assessed depression and apathy using the following methods. The Beck Depression Inventory Second Edition [67] and Hamilton Depression Rating Scale [68] were used to assess subjective and objective depressive symptoms. Both instruments include 21 items, with a maximum score of 63. Apathy was further evaluated using the Apathy Scale (14 items with a cut-off score of ≥ 16 and a maximum score of 42) [69, 70].

Dream-enactment behaviors and parkinsonism The patients were asked to complete the REM Sleep Behavior Disorder Screening Questionnaire-Japanese Version (RBDSQ-J), which consists of 13 questions (cut-off score: 5; maximum score: 13) [71, 72]. A modified Hoehn and Yahr Staging Scale was used to assess motor symptoms [73].

Olfactory test The Odor Stick Identification Test-Japanese, a valid Japanese olfactory test, was used [74]. Using 12 sticks with different odors, the respondents had to identify the correct odor from four options (maximum score, 12) with minimal false-negative or false-positive cut-off values (< 6 or < 4, respectively) for older patients [75].

Preliminary follow-up investigation and events definition

Following baseline evaluation, events during follow-up were observed through regular outpatient visits and a review of medical records. The patients visited the hospital every 1–4 months. It should be noted that the follow-up visits were not blinded as they were conducted by the same authors who conducted the semi-structured interviews (YS and HK).

The observed events included the following: a) phenoconversion, b) death, and c) fractures due to falls.

a) Phenoconversion: In the event of exacerbation of parkinsonism or cognitive decline during follow-up, the patient was referred to a trained neurologist (not the authors) who diagnosed them with PD, DLB, or MSA, all of which were defined as phenoconversion.
b) Death: In cases where a patient died during the follow-up period, the date and cause of death were collected.
c) Fractures due to falls: In patients with iRBD often experience falls. Therefore, information on fractures, which are a significant outcome of falls, was collected. During the follow-up period, if a patient experienced a fracture due to a fall, the date and details of the fracture were recorded.

Regarding the above (a–c), the progression-free survival period was defined as the date from baseline to the date of each event or "the censoring date" (February 5, 2024). Patients who dropped out during the follow-up were censored based on the date of their last visit. For patients who were transferred to another medical facility due to relocation or worsening of their condition, information following their transfer was not tracked.

Statistical analyses

Continuous variables are summarized as means and standard deviations, and categorical variables are summarized as counts and percentages. For between-group comparisons, continuous variables were compared using Student's t-tests. Categorical variables were compared using the chi-squared test. A logistic regression model was used to calculate the odds ratio with 95% confidence intervals for the risk of BT with iRBD. We conducted an unadjusted multivariate logistic regression (model 1) and adjusted for age and sex (model 2); age, sex, and comorbidity of hypertension (model 3); and age, sex, comorbidity of hypertension, and medication use (calcium blocker, angiotensin-converting enzyme or angiotensin II type inhibitor, or beta blocker) (model 4). Events during follow-up were assessed using Kaplan–Meier curves and log-rank tests. Sensitivity analysis was performed by excluding patients with arrhythmia to account for potential confounding by comorbid arrhythmia. The threshold for statistical significance was set at $p < 0.05$. To evaluate the pairwise differences, Cohen's effect size d was calculated and classified into small (d = 0.2), medium (d = 0.5), or large (r = 0.8) effect size. All statistical analyses were performed using MATLAB (version 2023a, MathWorks, Natick, MA, USA).

Results

The flowchart of the study is illustrated in Fig. 1. Of 55 eligible patients with iRBD, 48 underwent active standing tests. One patient was excluded from further analysis because of the inability to accurately measure BP owing to frequent arrhythmias during the test. Additionally, four patients who did not undergo DAT-SPECT were

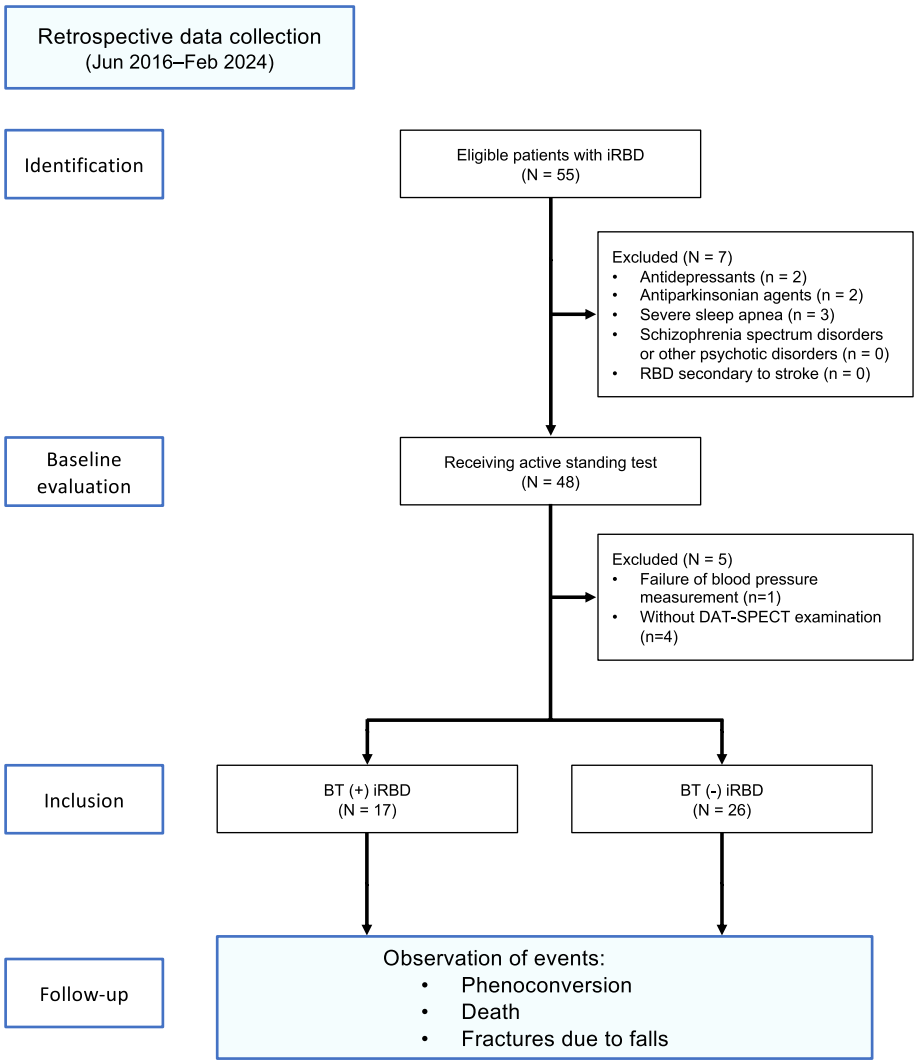

Fig. 1 Flowchart of the patients' inclusion and follow-up. Abbreviations: BP, blood pressure; HR, heart rate; BT, blunted tachycardia

excluded from the analysis. Consequently, the study included 43 patients with iRBD (mean age, 72.3 ± 7.9 years; 8 females). Among them, 17 patients (39.5%) met the criteria for BT, while 26 (60.5%) did not (details are described in 3.2 Active standing test section).

Demographic data

Table 1 presents the patients' demographic data, and supplementary information is summarized in Table S1. The analysis revealed a significantly higher age in the BT(+) group than in the BT(-) group ($p = 0.029$, Cohen's d = 0.692). The prevalence of comorbidities, such as hypertension and diabetes mellitus, was comparable between the groups. This finding extended to the use of medications for hypertension and proportion of patients using clonazepam; no significant differences were observed. The sensitivity analysis, excluding patients with arrhythmias, showed similar trends (Table S2, Table S3).

Active standing test

The active standing test results and HRV indices are presented in Table 2. There were no significant differences between the groups regarding sBP, dBP, or HR in the supine position. However, the changes in sBP, dBP, and HR upon standing differed significantly between the groups.

The decrease in sBP and dBP upon standing was more pronounced, and the increase in HR was blunted in the BT(+) group compared with in the BT(-) group. ΔHR/ΔsBP was significantly lower in the BT(+) group at 1, 2, and 3 min post-standing with large effect sizes. Fifteen

Table 1 Demographic data of the patients with isolated RBD with and without blunted tachycardia

	ALL ($n=43$)	BT (+) ($n=17$)	BT (-) ($n=26$)	*p*-value	Effect size BT (+)—BT (-)
Age [years]	72.3 ± 7.9	75.5 ± 3.1	70.2 ± 9.3	**0.029**	0.692
Sex (Female [n, %])	8 [18.6%]	2 [11.8%]	6 [23.1%]	0.351	N/A
Age at RBD onset [years]	63.6 ± 10.1	66.9 ± 7.8	61.5 ± 11.0	0.087	0.538
Comorbidity					
Hypertension [n, %]	16 [37.2%]	8 [47.1%]	8 [30.8%]	0.280	N/A
Coronary artery disease [n, %]	8 [18.6%]	5 [29.4%]	3 [11.5%]	0.141	N/A
Myocardial infarction [n, %]	2 [4.7%]	1 [5.9%]	1 [3.8%]	0.757	N/A
Diabetes mellitus [n, %]	8 [18.6%]	3 [17.6%]	5 [19.2%]	0.896	N/A
Arrhythmia [n, %]	4 [9.3%]	2 [11.8%]	2 [7.7%]	0.653	N/A
Atrial fibrillation [n, %]	5 [11.6%]	2 [11.8%]	3 [11.5%]	0.982	N/A
Hypercholesterolemia [n, %]	9 [20.9%]	3 [17.6%]	6 [23.1%]	0.669	N/A
Thyroid disease [n, %]	1 [2.3%]	0 [0%]	1 [3.8%]	0.413	N/A
Stroke [n, %]	5 [11.6%]	2 [11.8%]	3 [11.5%]	0.982	N/A

Abbreviations: *BT* blunted tachycardia, *RBD* rapid eye movement sleep behavior disorder

minutes after standing, the sBP and dBP of the BT(-) group generally returned to near-supine levels. In contrast, in the BT(+) group, sBP and dBP remained approximately 20 mmHg and 10 mmHg lower than the supine values, respectively (Fig. 2 (A2, B2)). The sensitivity analysis, excluding patients with arrhythmias, showed similar trends (Table S4, Figure S1).

Overall, 23.3% (10/43) of the patients met the criteria for OH, of whom 80% (8/10) were in the BT(+) group. Significantly more patients with BT(+) (47.1%, 8/17) met the criteria for OH (thus, they could be considered as having nOH) than those with BT(-) (7.7%, 2/26) ($p=0.003$, Table 2). Additionally, 32.6% (14/43) of the participants met the criteria for supine hypertension, with 35.3% (6/17) in the BT(+) group and 30.8% (8/26) in the BT(-) group.

Regarding HRV in the supine position, there were no significant differences between the groups across both time domain and Poincaré plot indices.

Clinical examinations

The clinical examinations are presented in Table 3, and supplementary information is summarized in Table S1. Regarding motor symptoms, all participants were classified as Hoehn and Yahr stage 0.

Regarding autonomic nervous function, no significant difference was observed in total SCOPA-AUT scores between the two groups. However, the urinary domain scores were significantly higher in the BT(+) group.

Nuclear medicine examinations revealed no significant differences in DAT accumulation between the groups. ^{123}I-MIBG myocardial scintigraphy was performed in 81.4% (35/43) of the patients, including 14 in the BT(+) group and 21 in the BT(-) group. All patients exhibited early H/M ratios below the normal threshold of 2.28, and 94% fell below the threshold for delayed H/M ratios of 1.91. When comparing the two groups, significantly lower accumulation in both early and delayed H/M ratios was noted in the BT(+) group, whereas no significant difference was observed in the washout ratio.

There were no significant differences in the olfactory test or cognitive function results between the groups. Furthermore, the prevalence of psychiatric symptoms, including noise pareidolia and minor hallucinations, did not differ significantly between the groups. All patients who experienced minor hallucinations at baseline maintained insight into their experiences with minor hallucinations.

While no significant difference was observed in RBDSQ-J scores between the two groups, a higher proportion of individuals in the BT(-) group exceeded the cut-off point.

The sensitivity analysis generally yielded similar results; however, it revealed a higher incidence of minor hallucinations in the BT(+) group, and no significant differences were observed in SCOPA-AUT Urinary scores (Table S3, Table S5).

Factors associated with BT

Table S6 presents the odds ratio for BT in the patients with iRBD. The sample size was limited; however, the following variables were significantly associated with BT after adjusting for age, sex, hypertension comorbidity, and medication use (model 4): years of education, exceeding the cut-off value of the RBDSQ-J score, early

Table 2 Results of the active standing test

	ALL (*n* = 43)	BT (+) (*n* = 17)	BT (-) (*n* = 26)	*p*-value	Effect size BT (+)—BT (-)
Systolic BP (mm Hg)					
Baseline	130.4 ± 16.8	130.9 ± 17.3	130.0 ± 16.9	0.874	0.049
ΔsBP at 1 min after standing	-11.0 ± 12.6	-20.0 ± 11.5	-5.2 ± 9.7	**< 0.001**	-1.391
ΔsBP at 2 min after standing	-8.7 ± 11.9	-16.7 ± 12.0	-3.5 ± 8.5	**< 0.001**	-1.288
ΔsBP at 3 min after standing	-9.1 ± 11.1	-17.3 ± 11.3	-3.8 ± 7.0	**< 0.001**	-1.480
Diastolic BP (mm Hg)					
Baseline	79.8 ± 9.0	81.0 ± 11.1	79.0 ± 7.4	0.486	0.215
ΔdBP at 1 min after standing	-3.4 ± 7.9	-8.7 ± 7.2	0.1 ± 6.2	**< 0.001**	-1.309
ΔdBP at 2 min after standing	-2.0 ± 8.1	-7.7 ± 8.2	1.8 ± 5.5	**< 0.001**	-1.405
ΔdBP at 3 min after standing	-2.5 ± 7.1	-7.7 ± 6.7	0.8 ± 5.1	**< 0.001**	-1.437
HR (bpm/min)					
Baseline	65.9 ± 9.4	67.0 ± 9.9	65.2 ± 9.3	0.562	0.179
ΔHR at 1 min after standing	5.8 ± 6.0	4.0 ± 3.7	7.0 ± 6.8	0.100	-0.516
ΔHR at 2 min after standing	5.7 ± 6.0	2.9 ± 3.1	7.5 ± 6.8	**0.014**	-0.788
ΔHR at 3 min after standing	5.5 ± 6.2	2.3 ± 3.1	7.7 ± 6.9	**0.004**	-0.926
ΔHR/ΔsBP (bpm/mm Hg)					
ΔHR/ΔsBP at 1 min after standing[a]	0.66 ± 0.65	0.26 ± 0.21	1.01 ± 0.71	**< 0.001**	-1.357
ΔHR/ΔsBP at 2 min after standing[b]	1.03 ± 1.83	0.31 ± 0.39	1.85 ± 2.43	**0.019**	-0.890
ΔHR/ΔsBP at 3 min after standing[c]	0.93 ± 1.54	0.17 ± 0.15	1.57 ± 1.88	**0.004**	-0.983
Orthostatic hypotension [n, %]	10 [23.3%]	8 [47.1%]	2 [7.7%]	**0.003**	N/A
Spine hypertension [n, %]	14 [32.6%]	6 [35.3%]	8 [30.8%]	0.757	N/A
Heart rate variability					
SDNN (ms)[d]	18.3 ± 9.9	16.6 ± 10.5	19.2 ± 9.7	0.472	-0.255
RMSSD (ms)[d]	13.8 ± 9.1	14.4 ± 11.9	13.5 ± 7.4	0.765	0.106
pNN50 (%)[d]	1.9 ± 5.2	2.9 ± 7.5	1.3 ± 3.4	0.407	0.294
Poincaré plots, SD1 (ms)[d]	9.8 ± 6.4	10.2 ± 8.4	9.5 ± 5.2	0.765	0.106
Poincaré plots, SD2 (ms)[d]	23.8 ± 12.8	21.0 ± 12.4	25.3 ± 13.0	0.355	-0.329
Poincaré plots, SD1/SD2[d]	0.41 ± 0.14	0.45 ± 0.16	0.39 ± 0.12	0.273	0.391

Abbreviations: *BT* blunted tachycardia, *BP* blood pressure, *sBP* systolic BP, *dBP* diastolic BP, *HR* heart rate, *SDNN* standard deviation of the NN intervals, *RMSSD* root mean square of successive differences, *pNN50* percentage of difference between adjacent normal. RR intervals greater than 50 ms, *SD1* Standard Deviation 1 of the Poincaré plot, *SD2* Standard Deviation 2 of the Poincaré plot

[a] Because ΔHR/ΔSBP was not calculated in patients with increased sBP at 1 min after standing, the number of patients was set to *n* = 34 for All, *n* = 16 for BT(+), and *n* = 18 for BT(-)

[b] Because ΔHR/ΔSBP was not calculated in patients with increased sBP at 2 min after standing, the number of patients was set to *n* = 30 for All, *n* = 16 for BT(+), and *n* = 14 for BT(-)

[c] Because ΔHR/ΔSBP was not calculated in patients with increased sBP at 3 min after standing, the number of patients was set to *n* = 37 for All, *n* = 17 for BT(+), and *n* = 20 for BT(-)

[d] Because of the exclusion due to comorbidity or measurement errors, *n* = 34 in All; *n* = 12 in BT(+); *n* = 22 in BT(-)

and delayed H/M ratio of ^{123}I-MIBG, MMSE score, and FAB score.

The sensitivity analysis, excluding patients with arrhythmias, generally yielded similar results; however, even after adjusting for various factors (model 4), DAT accumulation in the right striatum, OSIT-J score, and minor hallucinations remained significant (Table S7).

Phenoconversion, death, and fractures due to falls during short-term follow-up

Data regarding the follow-up events are summarized in Table 4 and Figure S2.

a) Phenoconversion

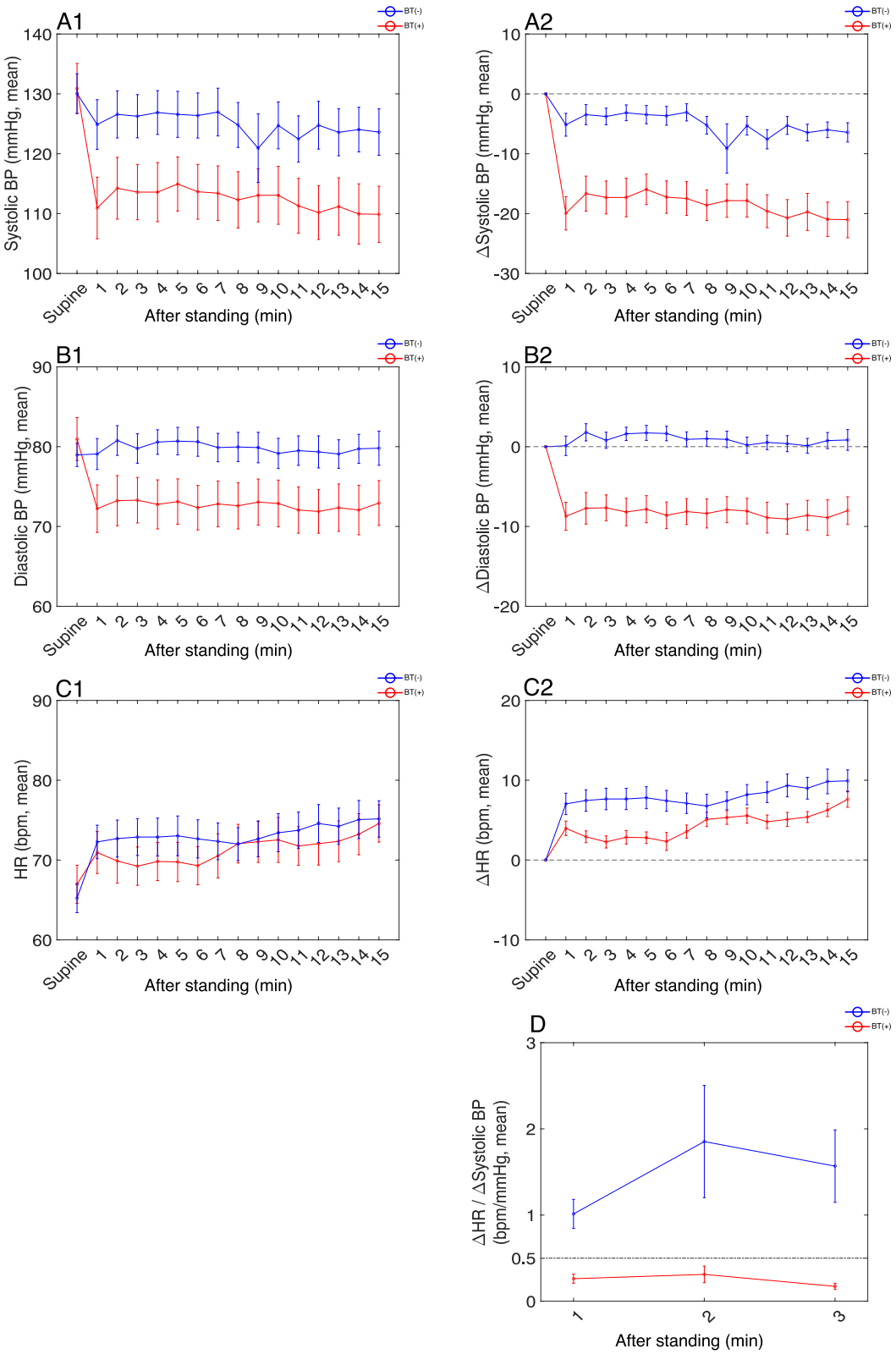

Fig. 2 Changes in BP, HR, and delta index during the active standing test. Comparison of the active standing test results in the BT(+) and BT(-) groups. (A1-C1) indicates absolute change (mean ± standard error of the mean); (A2-C2) indicates changes compared with the supine position (mean ± standard error of the mean); (D) indicates the changes in the BT criteria. Abbreviations: BP, blood pressure; BT, blunted tachycardia; HR, heart rate. x-axis: supine, mean value of the supine position, 1–15 min after standing

Table 3 Clinical examinations of the patients with isolated RBD with and without blunted tachycardia

	ALL (*n* = 43)	BT (+) (*n* = 17)	BT (-) (*n* = 26)	*p*-value	Effect size BT (+) -BT (-)
Autonomic nervous examination					
SCOPA-AUT, Total[a]	9.4 ± 6.9	11.8 ± 9.4	8.0 ± 4.5	0.086	0.549
Gastrointestinal[a]	2.7 ± 2.5	3.3 ± 3.1	2.4 ± 2.0	0.302	0.326
Urinary[a]	5.0 ± 2.9	6.1 ± 3.3	4.3 ± 2.4	**0.049**	0.633
Cardiovascular[a]	0.52 ± 0.97	0.75 ± 1.06	0.38 ± 0.90	0.240	0.372
Thermoregulatory[a]	0.50 ± 0.99	0.75 ± 1.29	0.35 ± 0.75	0.205	0.402
Pupillomotor[a]	0.29 ± 0.60	0.31 ± 0.60	0.27 ± 0.60	0.823	0.070
Sexual[a]	0.36 ± 1.14	0.56 ± 1.63	0.23 ± 0.71	0.368	0.284
DAT-SPECT					
Striatum, right	3.91 ± 1.31	3.80 ± 1.23	3.98 ± 1.37	0.668	-0.132
Striatum, left	3.92 ± 1.20	3.83 ± 1.13	3.98 ± 1.26	0.684	-0.126
Striatum, average	3.92 ± 1.22	3.81 ± 1.17	3.98 ± 1.27	0.668	-0.132
^{123}I-MIBG					
H/M, early[b]	1.52 ± 0.21	1.39 ± 0.13	1.61 ± 0.22	**0.003**	-1.089
H/M, early < 2.28 [n, %][b]	35 [100.0%]	14 [100.0%]	21 [100.0%]	N/A	N/A
H/M, delayed[b]	1.35 ± 0.31	1.18 ± 0.11	1.46 ± 0.34	**0.005**	-1.017
H/M, delayed < 1.91 [n, %][b]	33 [94.3%]	14 [100.0%]	19 [90.5%]	0.234	N/A
Washout ratio [%][b]	35.9 ± 11.3	40.3 ± 16.0	33.0 ± 5.5	0.063	0.648
Cognitive function					
MMSE score	28.0 ± 2.3	27.2 ± 3.0	28.4 ± 1.4	0.106	-0.506
MMSE score < 24 [n, %]	2 [4.7%]	1 [5.9%]	1 [3.4%]	0.757	N/A
FAB score	15.3 ± 2.3	14.8 ± 2.3	15.5 ± 2.2	0.356	-0.286
FAB score < 12 [n, %]	2 [4.7%]	1 [5.9%]	1 [3.4%]	0.757	N/A
MoCA score	24.7 ± 2.8	24.4 ± 2.8	25.0 ± 2.9	0.535	-0.192
MoCA score < 23 [n, %]	9 [20.9%]	5 [29.4%]	4 [15.4%]	0.269	N/A
Psychiatric symptoms					
Minor hallucinations [n, %]	18 [41.9%]	10 [58.8%]	8 [30.8%]	0.068	N/A

Abbreviations: *BT* blunted tachycardia, *SCOPA-AUT* the Scale for Outcomes in Parkinson's disease for Autonomic symptoms, *DAT-SPECT* dopamine transporter-single-photon emission computed tomography, *^{123}I-MIBG* ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, *H/M* heart-to-mediastinum, *MMSE* Mini-Mental State Examination, *FAB* Frontal Assessment Battery, *MoCA* Montreal Cognitive Assessment

[a] Because of missing data, *n* = 42 in All; *n* = 16 in BT(+); *n* = 26 in BT(-)

[b] Because of missing data, *n* = 35 in All; *n* = 14 in BT(+); *n* = 21 in BT(-)

Overall, 14 (32.6%) individuals experienced phenoconversion (seven PD and seven DLB) with no progression to MSA. Among those with BT(+), seven (41.2%) achieved phenoconversion (two with PD and five with DLB), with three dropouts during follow-up (due to relocation, self-discontinuation of outpatient visits, and death from cancer). Among those with BT(-), seven (26.9%) reached phenoconversion (five PD and two DLB), with four dropouts during follow-up (one self-discontinuation of outpatient visits and three deaths due to cancer).

b) Death

In total, six (14.0%) individuals died. Among those with BT(+), three (17.6%) died. The causes of death were pneumonia (*n* = 1, progression to PD), tuberculosis (*n* = 1, progression to DLB), and cancer (*n* = 1, not phenoconverted), with three dropouts during follow-up (due to relocation, hospitalization for comorbidities, and self-discontinuation of outpatient visits). Among those with BT(-), three (11.5%) died. The causes of death were pneumonia (progression to PD) in one case and cancer (not phenoconverted) in two, with four dropouts during follow-up (one self-discontinuation of outpatient visits, one hospitalization for worsened DLB, and two relocations).

c) Fractures due to falls

Table 4 Summary of the follow-up events

Events	All ($n=43$)	BT (+) ($n=17$)	BT (-) ($n=26$)	*p*-value
a) Phenoconversion				
Number of events [n (%)]	14 (32.6%)	7 (41.2%)	7 (26.9%)	
	(7 PD, 7 DLB)	(2 PD, 5 DLB)	(5 PD, 2 DLB)	
Dropout [n (%)]	7 (16.3%)	3 (17.6%)	4 (15.4%)	
Follow-up duration [years]	3.39 ± 2.43	3.39 ± 2.86	3.15 ± 2.14	0.429
b) Death				
Number of events [n (%)]	6 (14.0%)	3 (17.6%)	3 (11.5%)	
Dropout [n (%)]	7 (16.3%)	3 (17.6%)	4 (15.4%)	
Follow-up duration [years]	3.98 ± 2.32	4.22 ± 2.84	3.82 ± 1.95	0.585
c) Fractures due to falls				
Number of events [n (%)]	2 (4.7%)	1 (5.9%)	1 (3.8%)	
Dropout [n (%)]	11 (25.6%)	5 (29.4%)	6 (23.1%)	
Follow-up duration [years]	3.91 ± 2.30	4.13 ± 2.84	3.76 ± 1.92	0.585

Abbreviations: *BT* blunted tachycardia, *PD* Parkinson's disease, *DLB* dementia with Lewy bodies

Two (4.7%) individuals experienced fractures due to falls. Among those with BT(+), one (6.5%) fell and fractured the knee. He had already progressed to DLB by the time of the fall, with five dropouts during follow-up (one relocation, one self-discontinuation of outpatient visits, and three deaths). Among those with BT(-), one (3.9%) fell and sustained a skull fracture and traumatic brain injury. This patient had already progressed to DLB by the time of the fall, with six dropouts during follow-up (one self-discontinuation of outpatient visits, one relocation, one hospitalization for worsened DLB, and two deaths).

In all cases (a, b, and c), there was no significant difference in the follow-up duration between the BT(+) and BT(-) groups (Table 4). Figure S2 illustrates the Kaplan–Meier survival curves with the results of the log-rank tests and hazard ratios related to the incidence of phenoconversion, death, and fractures due to falls. BT was not a significant risk factor for any event.

The analysis about follow-up events, excluding patients with arrhythmias, showed similar trends (Table S8, Figure S3).

Discussion

To the best of our knowledge, this is the first study to elucidate the clinical and diagnostic features of patients with iRBD exhibiting BT, including nuclear medicine examinations. Approximately 40% of patients in our cohort met the criteria for BT, and approximately half of these patients also met the criteria for OH during the active standing test. The patients in the BT(+) group tended to be older and exhibited lower ^{123}I-MIBG uptake values. However, there were no significant differences between the BT(+) and BT(-) groups concerning DAT-SPECT uptake. The characteristics observed in the BT(+) iRBD group in this study were consistent with findings from research on patients with PD, where the severity of autonomic dysfunction does not correlate with the extent of dopaminergic neurodegeneration or motor symptom [76]. During the longitudinal follow-up, approximately one-third of all patients phenoconverted, 15% died, and 5% had fractures due to falls. In the preliminary longitudinal survey, no significant differences were observed in the risks of these events between the two groups. To ensure the robustness of the analysis results, a sensitivity analysis was conducted by excluding five patients with arrhythmias. The outcomes were largely consistent with those of the original analysis.

Our study provides evidence of decreased MIBG uptake in relation to BT in patients with iRBD. BT is considered a characteristic autonomic dysfunction reflecting cardiac sympathetic denervation. The severe autonomic dysfunction indicated by BT may suggest a more advanced progression of Lewy body pathology in the brain stem [77, 78]. While reduced ^{123}I-MIBG uptake in the early stages of PD has been reported to be associated with poor prognosis [35], our preliminary longitudinal investigation did not demonstrate an association between BT and specific events. Considering the prevalence of iRBD in older patients, our findings underscore the importance of considering non-neurological conditions, such as cancer, in long-term clinical management that may impact life expectancy. Future research could include conducting more extensive long-term follow-ups in a larger cohort of patients with iRBD to comprehensively ascertain the relationship between BT and long-term outcomes.

Demographic and clinical examination

OH is not only a common condition in older adults related to neurodegenerative diseases but can also be induced by medications, diabetes, and cardiovascular diseases [21, 24]. Given the prevalence of iRBD in middle-aged and older adults [3, 4], it is crucial to consider these comorbidities and medications when evaluating OH in this population. BT has been identified as a feasible method for detecting nOH [30].

Our findings revealed that approximately 40% (17/43) of the patients with iRBD exhibited BT during the active standing test. Patients in the BT(+) group were older and showed a more significant reduction in MIBG uptake. Logistic analysis, adjusted for age, sex, comorbidities, and medication use, indicated that MIBG uptake values, along with MMSE and FAB scores, were associated with BT. This suggests that BT is linked to abnormalities in postganglionic cardiac chronotropic responses, underscoring its significance in the context of neurodegeneration. Pronounced decline in MIBG uptake in iRBD with BT may have clinical relevance and potentially serve as a marker for more severe autonomic responses. The sensitivity analysis demonstrated a correlation between BT and minor hallucinations, as well as reduced accumulation of DAT in the right striatum and decreased olfaction (Table S7). These findings suggest that BT is associated with the potential progression of neurodegeneration.

The association between BT and cognitive decline aligns with that reported in a study on α-synucleinopathies, suggesting a link between BP regulation and cognitive impairment [26]. Furthermore, a lower proportion of patients in the BT(+) group exceeding the RBDSQ-J cut-off score reflected the temporal changes in RBD symptoms, including symptom alleviation or disappearance with neurodegenerative disease progression [79, 80].

This study's significance is further enhanced by the concurrent use of ^{123}I-MIBG and DAT-SPECT, a methodology not widely adopted in iRBD research to date. Notably, the large-scale longitudinal study by Miyamoto T. and Miyamoto M. (306 patients with iRBD) [81] represents a significant investigation in this field. In contrast, other existing literature contains limited studies incorporating ^{123}I-MIBG to investigate iRBD, with cross-sectional analyses reporting sample sizes of 108 [14] and 32 [33], and longitudinal studies documenting sample sizes of 36 [82] and 40 [83].

In previous studies, reduced ^{123}I-MIBG uptake has been shown to qualitatively support the presence of Lewy body pathology in iRBD [15, 16]. Additionally, the large-scale study by Miyamoto T. and Miyamoto M. in 2024 [81] demonstrated a progressive decline in ^{123}I-MIBG uptake in 33 patients with iRBD who underwent follow-up, with those exhibiting reduced uptake progressing to PD or DLB, while those without reduced uptake progressed to MSA. This study highlights the quantitative significance of ^{123}I-MIBG uptake in tracking disease progression.

In our study, the BT(+) showed a more pronounced reduction in ^{123}I-MIBG uptake. After adjusting for age and sex, BT remained significantly associated with ^{123}I-MIBG uptake levels. These results suggest that ^{123}I-MIBG is not only qualitatively but also quantitatively significant in iRBD. The majority of patients exhibited ^{123}I-MIBG uptake below the cutoff value, aligning with previous qualitative findings [15, 16]. Our study did not find an increased risk of phenoconversion or mortality in the BT(+) group within our limited sample size and follow-up period. However, considering the findings of the longitudinal ^{123}I-MIBG follow-up study [81], a more significant reduction in ^{123}I-MIBG uptake in iRBD may indicate the progression towards PD or DLB. To confirm whether BT is associated with ^{123}I-MIBG uptake reductions related to PD or DLB, it will be necessary to conduct longitudinal follow-up studies of ^{123}I-MIBG and BT assessments using active standing or postural tests.

Our investigation sets a new precedent by executing DAT-SPECT across all 43 patients, ^{123}I-MIBG in 35 patients, and longitudinal follow-up. Our study provides nuclear medical insights pertinent to iRBD, thereby advancing the understanding of the neurodegenerative diseases.

Active standing test

OH is a prevalent symptom among older adults and has serious prognostic implications for patients with neurodegenerative diseases set the stage for our investigation [21]. Recent advancements have shown that BT during a tilt test can accurately detect nOH [30].

The North American Prodromal Synucleinopathy (NAPS) Consortium's cross-sectional study on a large cohort of patients with iRBD indicated a commonality of nOH within this population, revealing that 27% met the criteria for OH, with 77% of them exhibiting reduced HR augmentation ($\Delta HR/\Delta sBP < 0.5$) [32]. This suggests a potentially widespread prevalence of nOH among patients with iRBD. Furthermore, the consortium highlighted that patients with OH (with or without BT) demonstrated a significant presence of supine hypertension (approximately 70%), indicating abnormalities in BP regulation both during standing and at rest. Our previous study underscored the diminished HRV during spine positioning in patients with iRBD compared with in healthy controls, suggesting the predictive value of HRV metrics for subsequent OH occurrence [8].

The strength of the current study lies in the successful implementation of a standardized protocol for the active standing test, allowing the observation of BP and HR fluctuations over 15 min after standing and the identification of delayed BP drops. We observed that 23.3% (10/43) of the patients met the criteria for OH, and 80% (8/10) of these patients fulfilled the criteria for BT. This proportion aligns closely with the findings of the NAPS Consortium [32]. While the comorbidity of hypertension was 37.2% (16/43) of our study population (Table 1), only 32.6% (14/43) met the criteria for supine hypertension, with no significant differences of supine hypertension between the BT (+) and BT (-) groups. There were also no differences between the groups in terms of the HRV time-domain metrics or Poincaré plot indices at rest. These observations suggest that the pathophysiology of BT, detected during the active standing test, may not be easily discernible at rest.

In our previous study, which included some patients from the current study, we observed that resting HRV in patients with iRBD was significantly attenuated compared to healthy controls [8]. Specifically, reductions in RMSSD, pNN50, SD1, and SD2 indicated diminished parasympathetic function, while the decrease in SDNN suggested a concurrent reduction in both sympathetic and parasympathetic functions [50, 84, 85] In the present study, the H/M ratio of ^{123}I-MIBG was observed to be reduced across the entire group of patients with iRBD, with a further reduction in the BT(+) group compared to the BT(-) group. These findings suggest that even within the iRBD population characterized by reduced autonomic function, BT is more likely to be present in individuals with more pronounced sympathetic dysfunction.

The results of the "15 min after standing" of the active standing test are pivotal for understanding the BP dynamics in patients with iRBD. Even after compensatory mechanisms should have adjusted to postural changes [86], the BT(+) group exhibited lower sBP and dBP than their supine measurements, suggesting that supine BP is usually relatively high. This indicates the influence of supine hypertension and underscores the necessity of evaluating BP regulation across different postures for a more comprehensive assessment of autonomic dysfunction. Therefore, further research considering the comorbidities and treatment status (the extent of hypertension control) is needed to accurately evaluate the neurodegenerative impact.

The BT(+) group had a higher proportion of patients with OH than the BT(-) group (47.1% vs. 7.7%, $p=0.003$). The pronounced decline in MIBG uptake in the BT(+) group underscores the potential clinical relevance and quantitative relationship between MIBG uptake and clinical manifestations [87]. Future research should focus on multifaceted assessments to unravel the nuanced interplay between BP regulation, HRV, and neurodegenerative disease progression.

Preliminary longitudinal follow-up

In this study, patients with iRBD with and without BT were followed up to investigate significant outcomes, including phenoconversion, death, and trauma-related falls, particularly fractures. Systematic reviews and meta-analyses identified OH as a risk factor for phenoconversion to PD in patients with iRBD [88]. Furthermore, BT has been suggested as a predictive factor for the progression from pure autonomic failure to PD [31]. OH is associated with increased mortality and trauma-related falls in patients with PD and DLB [24, 25, 27]. Overall, it is crucial to consider these events in patients with iRBD, not only for phenoconversion but also for mortality and trauma-related falls.

Phenoconversion occurred in 41.2% of the patients in the BT(+) group compared with 26.9% in the BT(-) group. Among the patients in the BT(+) group, progression to DLB was more common (two PD and five DLB cases), whereas patients in the BT(-) group were more likely to progress to PD (five PD and two DLB cases). None of the cases progressed to MSA. There was no significant difference in the risk of phenoconversion, death, or fall-related fractures between the two groups (Figure S2).

The limited sample size and follow-up duration may have contributed to the lack of statistical power to detect differences between the events, warranting further investigation. Patients in the BT(+) group were more likely to progress to DLB than those in the BT(-) group, suggesting that individuals exhibiting BT at the iRBD stage, indicative of more pronounced autonomic dysfunction, are more prone to progression to DLB. Our observations align with the notion that autonomic dysfunction is more pronounced in patients with DLB than in those with PD [89]. This is supported by logistic regression results linking BT with cognitive decline, suggesting an association between BT and phenoconversion to DLB.

These causes of death highlight the need to focus on common issues among older adults. Those who progressed to PD or DLB died of pneumonia or tuberculosis, whereas those who did not progress died of cancer. Although OH in patients with PD and DLB has been reported to be related to life prognosis [24, 25, 27], iRBD spans years to decades before phenoconversion [2, 7]. The long-term life prognosis in iRBD may be influenced independently or synergistically by neurodegenerative issues and common older adult conditions such as tumors and infections. Fractures due to falls were rare; however, both cases progressed to DLB. A possible link

has been suggested between DLB-associated parkinsonism, attentional and visuospatial impairments, and fatal falls [90, 91].

Limitations

This study has some limitations. First, the small sample size and the fact that the study was conducted at a single center may limit the generalizability of our findings. Furthermore, due to the exploratory nature of the current study, an a priori calculation of sample size was not performed, which could potentially limit the ability to identify significant associations.

Second, the follow-up period was limited to an average of 3–4 years. The longitudinal investigation in this study is considered preliminary due to the small sample size and short follow-up period. While it might take up to a decade to observe a significant number of patients with iRBD undergoing phenoconversion [2, 7], in this study, approximately one-third of the patients phenoconverted, indicating that the follow-up duration was not negligible. Nonetheless, there was a notable dropout rate during the follow-up period, including patients who died or were admitted to multiple institutions owing to worsening physical conditions. In studies involving older participants, an extended follow-up period may increase the dropout rates owing to issues specific to this population, such as cancer. Hence, a 3- to 4-year follow-up period may be considered reasonable.

Another limitation of this study is the lack of longitudinal assessment for BP and HR after standing, which were evaluated at a single time point. Moreover, this study used the active standing test instead of the tilt-table test to define BT. The active standing test, which is considered a natural movement in daily life that imposes less burden on patients, is ethically favorable. Previous studies on nOH and BT in patients with iRBD have also employed the active standing test to ensure consistency in methodology [32].

Another limitation is the focus on BT rather than nOH for patient classification. OH can occur from a complex interplay of factors, including cardiovascular diseases, and not solely from neurodegenerative diseases [21, 24]. At the early stages of a neurodegenerative disease, such as iRBD, focusing on BT may allow for a more direct assessment of neurodegenerative pathology.

Notably, in our patient cohort, 47.1% (8/17) of patients with BT also had OH (thus, having nOH), which is significantly higher more than those without BT ($p=0.003$, Table 2). Given that only eight patients met the criteria for nOH, the statistical analysis was limited. Despite the small sample size in this study, future studies categorizing patients based on the presence or absence of BT and OH may prove beneficial.

Conclusions

In this study, approximately 40% of the patients with iRBD exhibited BT during the active standing test. Even after adjusting for age, sex, comorbidities, and medication use, BT was significantly associated with reduced MIBG uptake. We have identified the possibility that BT in iRBD reflects cardiac sympathetic neurogenic denervation. Moreover, our findings suggest that reduced ^{123}I-MIBG uptake may be quantitatively significant in assessing the severity of autonomic dysfunction in iRBD. However, the preliminary longitudinal follow-up did not clearly establish a relationship between BT and events such as phenoconversion, death, or fractures due to falls. Future research is needed to elucidate the potential prognostic value of BT.

Abbreviations

BT	Blunted tachycardia
dBP	Diastolic blood pressure
DLB	Dementia with Lewy bodies
FAB	Frontal Assessment Battery
H/M	Heart-to-mediastinum
HRV	Heart rate variability
iRBD	Isolated rapid eye movement sleep behavior disorder
MMSE	Mini-Mental State Examination
MSA	Multiple system atrophy
nOH	Neurogenic orthostatic hypotension
OH	Orthostatic hypotension
PD	Parkinson's disease
RBD	Rapid eye movement sleep behavior disorder
RBDSQ-J	REM Sleep Behavior Disorder Screening Questionnaire-Japanese Version
RRI	R-R interval
SCOPA-AUT	Scale for Outcomes in PD-Autonomic
sBP	Systolic blood pressure

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03822-w.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

Shota Saeda: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing. Yukiyoshi Sumi: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Funding acquisition. Koichi Fujiwara: Writing - Review & Editing, Supervision. Hiroshi Kadotani: Investigation, Writing - Review & Editing, Funding acquisition.

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Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Shiga University of Medical Science (R2017-199). This study was part of the investigation into risk factors for phenoconversion and also had been approved by the committee (R2017-160). Written informed consent to participate was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

Hiroshi Kadotani was supported by donations from Fukuda Life Tech Co., Ltd., Fukuda Life Tech Keiji Co., Ltd., and Kadotani Kids Clinic to the Shiga University of Medical Science. Hiroshi Kadotani received Merck Sharp and Dohme Corp/MSD K.K. (the Investigator-initiated Studies Program), Eisai Co., Ltd., and the SECOM Science and Technology Foundation. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp and Dohme Corp/MSD K.K. The other authors declare no conflicts of interest.

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