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Association of Cardiovascular Autonomic Failure With Progression and Phenoconversion in Isolated REM Sleep Behavior Disorder

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Abstract

Background and Objectives

Isolated REM sleep behavior disorder (iRBD) is a prodromal state of α-synucleinopathies, presenting years before overt neurodegenerative disorders. Autonomic nervous system (ANS) involvement, particularly cardiovascular autonomic failure, may indicate progression. However, its role as a (multidimensional) marker for disease progression and phenoconversion remains unclear. This study aimed to investigate whether cardiovascular autonomic failure and symptoms of autonomic dysfunction serve as multidimensional markers in patients with iRBD.

Methods

We conducted a prospective cohort study of patients with iRBD (iRBDs) and controls. Participants underwent cardiovascular reflex tests (CRTs) with beat-to-beat monitoring of blood pressure (BP) and ANS symptom assessments at baseline and annually. Primary outcomes were prevalence and progression of cardiovascular autonomic failure and the risk factors of phenoconversion. Longitudinal changes were evaluated through mixed-effects regression, predictors associated with conversion with Cox regression analysis.

Results

Sixty-four iRBDs (mean age 68.89 ± 6.75 years, 75% male) and 67 controls (66.57 ± 7.91 years, 68% male) were recruited. At baseline, iRBDs exhibited a prevalent sympathetic cardiovascular dysfunction, with more frequent neurogenic orthostatic hypotension (nOH in 9 iRBDs) and abnormal BP responses to CRTs (pathologic Valsalva maneuver [VM] overshoot in 27 iRBDs). Longitudinal data demonstrated progressive deterioration of sympathetic baroreflex function, with increased prevalence of nOH (7 iRBDs with incident nOH; yearly odds ratio [OR] = 2.44) and deterioration of parasympathetic cardiovagal function. Thirteen patients (20.3%) phenoconverted to α-synucleinopathies. Neurogenic OH (hazard ratio [HR] = 5.05), altered sympathetic baroreflex function (pathologic VM HR = 3.49), and blunted parasympathetic cardiovagal responses (pathologic deep breathing heart rate ratio HR = 3.27) were significant risk factors for phenoconversion; their early appearance 5 years from iRBD onset increased the conversion risk, up to 4-fold. Symptoms of autonomic failure were more prevalent in iRBD and deteriorated over time but failed to predict conversion.

Discussion

Progressive deterioration of cardiovascular autonomic function is a feature of iRBDs and affects the risk of phenoconversion. Limitations include the relatively short follow-up period and small number of converters. This study highlights the importance of objective cardiovascular autonomic testing as a multidimensional marker for risk stratification in iRBD.

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Supplementary Material

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Glossary

^{123I}MIBG = ^{123}I-metaiodobenzylguanidin; **ANS** = autonomic nervous system; **BP** = blood pressure; **COMPASS-31** = Composite Autonomic Symptom Score-31; **CRT** = cardiovascular reflex test; **DB** = deep breathing; **DBP** = diastolic BP; **DLB** = dementia with Lewy bodies; **HC** = healthy control; **HR** = heart rate; **HUTT** = head-up tilt test; **iAF** = isolated autonomic failure; **IQR** = interquartile range; **iRBD** = isolated REM sleep behavior disorder; **MDS-UPDRSIII** = Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III; **MSA** = multiple system atrophy; **nOH** = neurogenic orthostatic hypotension; **OR** = odds ratio; **PD** = Parkinson disease; **SBP** = systolic BP; **SCOPA-AUT** = Scales for Outcomes in Parkinson's Disease–Autonomic; **VM** = Valsalva maneuver; **vPSG** = video-polysomnography; **VR** = Valsalva ratio.

Introduction

Isolated REM sleep behavior disorder (iRBD) is a well-recognized prodromal state of an underlying α-synucleinopathy, occurring several years before the conversion to an overt neurodegenerative disorder and indicating that neurodegeneration of specific brainstem nuclei has already started. Patients with iRBD can manifest subtle motor (i.e., parkinsonian and cerebellar) and nonmotor (e.g., hyposmia, autonomic, and cognitive) signs and symptoms, which may represent clinical markers, that, in combination with instrumental and laboratory markers, reflect not only the increase of the neurodegenerative burden but also the risk of phenoconversion.[1] The search for such markers and their progression is pivotal both in providing patients with appropriate counselling regarding their prognosis, as well as to stratify patients in the context of trials aimed at identifying neuroprotective therapies.[2,3]

The involvement of the autonomic nervous system (ANS) plays an important role when we consider that also isolated autonomic failure (iAF) may be a peripheral premotor/precognitive state of overt CNS α-synucleinopathies.[4] Moreover, cardiovascular autonomic failure and genitourinary dysfunction are core clinical features of multiple system atrophy (MSA)[5] and supportive feature of Parkinson disease (PD)[6] and dementia with Lewy bodies (DLB).[7] In iRBD, cardiovascular autonomic failure may be of both central and peripheral origin, the first arising after degeneration of neighboring nuclei at the ponto-midline level (i.e., dorsal nucleus of the vagus and nucleus ambiguus) and supported by imaging evidence,[8] the second demonstrated by pathology[9] and nuclear medicine studies, showing postganglionic cardiac denervation.[10,11]

Up to 80% of patients with iRBD show subjective impairment of at least 1 autonomic domain, while objective studies on cardiovascular autonomic failure mainly come from retrospective,[12] case-control studies,[13] or addressing other at-risk populations.[14] Thus, it is still ambiguous whether autonomic impairment, and in particular, cardiovascular autonomic failure is an intrinsic factor of iRBD or can represent a versatile marker for progression and conversion toward α-synucleinopathies.

Within this framework, in this prospective cohort study of patients with iRBD, we aimed to explore the usefulness of objectively evaluated cardiovascular autonomic failure[15] and other symptoms of autonomic impairment as a multidimensional marker, verifying (1) their prevalence and characteristics in defining the clinical picture of patients with iRBD (state marker), (2) their progression over time (monitoring marker), and (3) their association with a higher risk of phenoconversion (prognostic marker).

Methods

Participants' Selection

We consecutively recruited patients referred to the sleep center of our department from April 2017 to March 2023 with a diagnosis of iRBD, confirmed by video-polysomnography (vPSG)[16,17] and normal brain MRI evaluation. Exclusion criteria were (1) a Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRSIII) score >6 (excluding action and postural tremor),[18] (2) a positive history of severe or secondary ANS impairment (e.g., diagnosed iAFs with RBD, heart failure, severe valvular or coronary disease, and uncontrolled diabetes mellitus), or (3) clinically relevant cognitive impairment (i.e., loss of activities of daily living and mild cognitive impairment[19] at cognitive tests[20]). RBD onset was evaluated based on the patient recollection of the first "major" episode.[21]

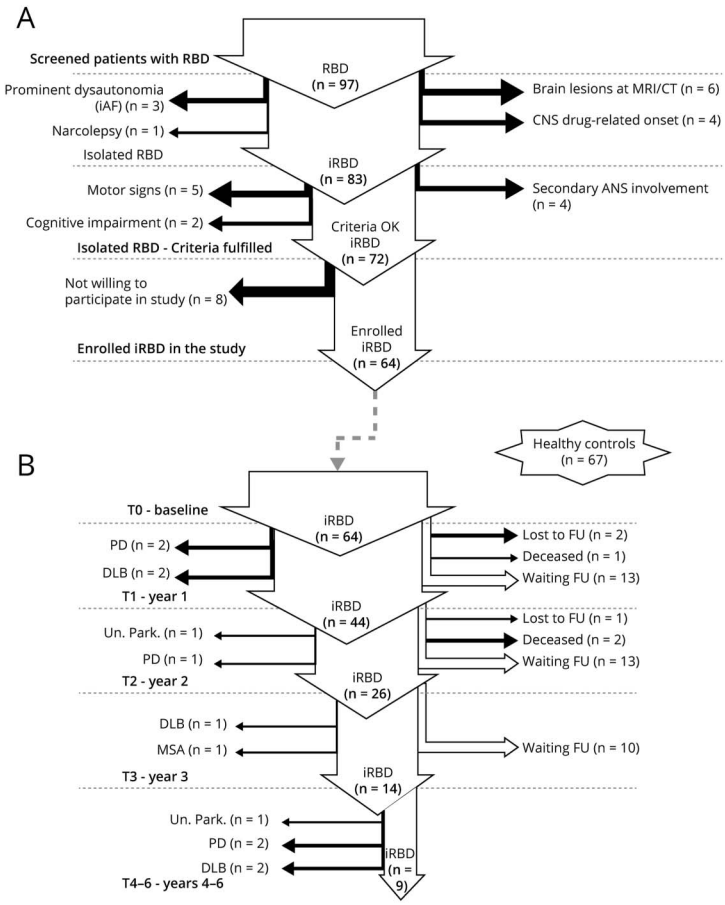
Spouses or nonconsanguineous acquaintances of patients with iRBD, comparable in age, sex, and comorbidities, were selected as control group after exclusion of RBD through vPSG and neurologic involvement of CNS, history of ANS dysfunctions, and of motor and cognitive impairment.

From a total 97 screened participants, 64 fulfilled inclusion criteria and willingly accepted to participate in the study (Figure 1).

Study Protocol

The protocol included a baseline standardized assessment of the autonomic control of the cardiovascular system (Ewing test battery for cardiovascular reflexes [CRT]),[15,22] and the collection of symptoms of ANS involvement through a semi-structured interview, the Scales for Outcomes in Parkinson's Disease–Autonomic (SCOPA-AUT),[23] and the Composite Autonomic Symptom Score-31 (COMPASS-31)[24] questionnaires (see eAppendix 1: Protocol Details for methodological details). Cardiovascular autonomic failure was defined in the presence of a pathologic Valsalva maneuver (VM).

Figure 1 Cohort Structure and Instrumental Follow-Up of Patients With iRBD*



Part (A) describes the workflow (arrows) of selection from screened RBD patients to patients with iRBD finally enrolled in the study. Part (B) describes participant flow through the instrumental timepoints, endpoint outcomes are listed on the left, other outcomes, dropouts, and patients waiting for the next timepoint on the right. DLB = dementia with Lewy bodies; FU = follow-up; iRBD = isolated REM sleep behavior disorder; MSA = multiple system atrophy; PD = Parkinson disease; T0…T4-6 = baseline (T0) and planned subsequent instrumental yearly follow-ups; Un. Park. = not yet defined form of atypical parkinsonism. *iRBD was considered, as per the International Classification of Sleep Disorders, third edition,[17] when occurring without any association with other diseases, particularly neurodegenerative conditions, at the time of diagnosis. RBD was classified as secondary when associated with other disorders or causes such as narcolepsy, neurodegenerative disease, brain lesions, drug use, or withdrawal, and autoimmune disorders.

Patients repeated CRTs and the standardized collection of clinical autonomic data every year (i.e., instrumental follow-up), as well as new symptom onset, up to the time of phenoconversion or last follow-up (i.e., clinical follow-up). Cardiac ^{123}I-metaiodobenzylguanidin (^{123I}MIBG)-SPECT was performed once during the disease course to elucidate the peripheral involvement in case of cardiovascular autonomic failure. Patients and/or their relatives were contacted by telephone and questioned about the clinical course and the time and cause of death (if applicable) when the patient missed a clinical evaluation within the 12 months.

The data obtained from these assessments were compared with normative laboratory values and the data from patients with those from controls. In relation to progression, each patient's result was compared with data at follow-up. Survival data were defined based on time to conversion or death (if the patient died before phenoconversion) from disease onset. Three neurologists (G.C.-B., P.C., and L.S.) suggested the final diagnosis of iRBD, PD, DLB, or MSA, based on data review at last evaluation.[5-7] This diagnosis was considered definitive with fulfillment of the highest level of certainty for the specific diagnostic criteria and only in the presence of full diagnostic agreement between the 3 experts; otherwise, it was considered as undefined atypical parkinsonism or dementia, based on the prominent clinical feature developed by the patient.

Cardiovascular Reflex Tests

CRTs were performed in the morning, starting at 8:00 AM for all participants, in a temperature-controlled clinical investigation room (23 ± 1°C).[15,20] Participants had been drug-free, for drugs with effect on the cardiovascular system, overnight and those on prolonged-release agents discontinued them for the necessary amount of time to allow proper washout.

CRTs were performed under audio and video-polygraphic monitoring (ANScovery Modular System; SparkBio Srl, Bologna, Italy). The following parameters were monitored continuously: beat-to-beat blood pressure (BP) (Finometer Midi; Finapres Medical Systems, Amsterdam, the Netherlands), EKG, and abdominal breathing (Model 15LT; Grass Techonologies, Quincy, MA).[15]

After 30 minutes of supine rest, the following tests were performed: head-up tilt test (HUTT; 10 minutes at 65°), VM (forced expiratory pressure of 40 mm Hg maintained for 15

seconds), deep breathing (DB) test (6 breaths per minute), and isometric muscle exercise (sustained handgrip [HG] test one-third of maximal effort for 5 minutes). An adequate period of rest was allowed to reach basal BP and heart rate (HR) values in-between investigations. A specialized technician and an external device tutor monitor guided and supported participants and verified the correct execution of the tests. The technician asked the participants about symptoms of OH during HUTT.

The following parameters were calculated: (1) basal systolic BP (SBP), diastolic BP (DBP), and HR as the mean value of the last 5 minutes of supine rest preceding HUTT; (2) response to HUTT as the difference (delta [Δ]) between SBP, DBP, and HR values at the third and tenth minutes compared with basal; (3) ΔHR/ΔSBP ratio as the change in HR by the fall in SBP at the 3-minute mark upright and expressed as bpm/mm Hg (pathologic if ΔHR/ΔSBP <0.5)[25]; (4) Valsalva ratio (VR) = HR late phase II/HR phase IV of VM (pathologic if VR <1.25)[4,26]; (5) presence of BP recovery in late phase II of VM (ΔSBP [IIb-IIa]) = max SBP late phase II − min SBP early phase II (pathologic if ΔSBP [IIb-IIa] ≤0 mm Hg); (6) presence of overshoot in phase IV of VM = max BP phase IV (within 20 seconds after the strain release) − mean basal BP (pathologic if overshoot <10 mm Hg); (7) time of phase IV = time interval between the strain release and phase IV; (8) sinus arrhythmia during DB (i) (ΔIE) = average of the 10 shortest R-R intervals during inspiration − average of the 10 longest R-R during expiration and (ii) I/E ratio = ratio between the average of the 10 shortest RR intervals in inspiration and in expiration (pathologic if either ΔIE <8 bpm or I/E ratio <1.10); (9) response to HG as Δ compared with basal values of SBP, DBP, and HR after 5 minutes of isometric effort (pathologic if ΔDBP <10 mm Hg).

OH was defined according to consensus criteria[27] and classified as neurogenic orthostatic hypotension (nOH) in the absence of overshoot in phase IV of VM (pathologic VM). Supine hypertension in autonomic failure was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg, after 5 minutes of supine rest preceding HUTT.[28]

When HR could not be reliably assessed because of cardiac rhythm abnormalities, such as bi-trigeminy or atrial fibrillation, the neurogenic nature of OH could not be accurately determined because rhythm disturbances may have interfered with validity of overshoot evaluation and with beat-to-beat BP monitoring in a short time frame.

Age at OH onset was considered congruent to the age of orthostatic intolerance symptom onset if the patient exhibited these symptoms. In asymptomatic patients, OH onset was considered as the first time this condition was demonstrated at CRTs.

Database and Statistical Methods

The normality of the distribution of the continuous parameters was checked with the Skewness-Kurtosis test, and variables were expressed as the mean ± SD or median with interquartile ranges (IQRs) when appropriate. Categorical variables were described by their absolute and/or relative frequencies.

To investigate the differences between patients with iRBD and controls and between converters and nonconverters, the Student *t* test was used for the evaluation of normally distributed continuous numerical variables, the Mann-Whitney *U* test for nonnormally distributed and ordinal variables. The χ^2 test was used for the analysis of nominal variables.

Longitudinal test data were evaluated by means of mixed-effects regression, within linear or logistic regression models, considering the passage of time at subsequent follow-ups as independent variable to estimate the yearly progression rate of each variable of interest. Age at baseline was added as a correction covariate. Results were presented as β coefficients or odds ratios (ORs) with 95% CIs. Robust errors were computed for this analysis.

Kaplan-Meier curves were used to analyze the overall and related conversion survival and the log-rank test to compare survival between patient subgroups. Significant parameters differentiating converters and nonconverters at baseline and single variables of interest were tested with Cox regression analyses, with computation of robust errors, to identify variables associated with conversion to overt synucleinopathies. Parameters with a value of $p < 0.1$ on univariate analysis were entered into a multivariable model. A p value <0.05 was considered significant for all tests. Statistical analyses were performed using SPSS Statistics version 26 (IBM, Armonk, NY) and Stata SE version 17.0 (StataCorp LLC, College Station, TX).

Standard Protocol Approvals, Registrations, and Patient Consents

This study protocol was prepared in accordance with the Standards of Good Clinical Practice and was approved by the Bologna-Imola Interagency Ethics Committee (CE-BI, code 17036) on April 27, 2017. Patients and controls all gave their written informed consent to personal data processing for research purposes.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

Baseline Evaluation

Baseline Demographic Data

The 64 patients with iRBD (iRBDs) (48 [75.0%] male; median disease duration 4.63 [7.79–9.31] years) and the 67 healthy controls (HCs) (45 [68.2%] male) presented a comparable age ($p = 0.095$) (Table 1). No significant differences in cardiovascular drug usage or diseases affecting the cardiovascular system were noted (eTable 1).

Table 1 Baseline Demographic and Principal Autonomic Data of Patients With iRBD and Controls

Demographics	iRBD (n = 64)	HC (n = 67)	*p* Value
Sex, n (%)			
Male	48 (75.0)	45 (68.2)	0.323
Female	16 (25.0)	22 (32.8)	
Age at baseline, y, mean ± SD	68.89 ± 6.75	66.57 ± 7.91	0.095
Age at onset, y, mean ± SD	62.71 ± 7.77	—	—
Duration RBD T0, y, median (IQR)	4.63 (7.79 to 9.31)	—	—
BMI, kg/m^2, mean ± SD	27.09 ± 3.33	26.19 ± 3.70	0.075
Head-up tilt test	iRBD (n = 61)	HC (n = 67)	
SBP supine resting, mm Hg, mean ± SD	140.77 ± 20.72	131.01 ± 16.70	0.006
DBP supine resting, mm Hg, mean ± SD	70.70 ± 8.08	67.93 ± 9.15	0.072
HR supine resting, bpm, mean ± SD[a]	61.86 ± 9.44	64.34 ± 9.10	0.140
ΔSBP 3 min, mm Hg, mean ± SD	−9.36 ± 15.31	7.43 ± 11.11	<0.001
ΔDBP 3 min, mm Hg, mean ± SD	−0.95 ± 6.33	7.28 ± 5.88	<0.001
ΔHR 3 min, bpm, mean ± SD[a]	6.87 ± 5.41	9.03 ± 5.41	0.034
nOH, n (%)[a]	9 (16.7)	0 (0.0)	0.001
ΔHR/ΔSBP ratio, bpm/mm Hg, median (IQR)[a]	0.74 (0.35 to 1.53)	1.0 (0.45 to 2.00)	0.283
ΔSBP 10 min, mm Hg, mean ± SD	−9.61 ± 18.07	6.63 ± 10.90	<0.001
ΔDBP 10 min, mm Hg, mean ± SD	1.05 ± 6.87	7.45 ± 5.96	<0.001
ΔHR 10 min, bpm, mean ± SD[a]	7.84 ± 6.22	8.18 ± 5.54	0.550
Valsalva maneuver	iRBD (n = 54)	HC (n = 67)	
Overshoot, mm Hg, median (IQR)	8.50 (−7.00 to 24.00)	37.00 (24.00 to 48.00)	<0.001
Pathologic overshoot, n (%)	27 (50.0)	1 (1.5)	<0.001
VR, median (IQR)	1.30 (1.23 to 1.43)	1.59 (1.42 to 1.83)	<0.001
Pathologic VR, n (%)	15 (27.8)	7 (10.4)	0.013
Symptoms of autonomic impairment	iRBD (n = 57)	HC (n = 45)	
CV			
Orthostatic intolerance, n (%)	35 (61.4)	13 (28.9)	0.001
Syncope in past 6 mo, n (%)	3 (5.3)	2 (4.4)	0.611
GI			
Mild dysphagia, n (%)	13 (22.8)	3 (6.7)	0.023
Constipation, n (%)	18 (31.6)	4 (8.9)	0.005
Sialorrhea, n (%)	5 (8.8)	2 (4.4)	0.327
UR			
Nocturia, n (%)	10 (17.5)	4 (8.9)	0.166
Urinary urgency, n (%)	21 (36.8)	11 (24.4)	0.130
Urinary incontinence, n (%)	12 (21.1)	4 (8.9)	0.078
PM: Pupillary dysfunction, n (%)	20 (35.1)	6 (13.3)	0.010
TR: Thermoregulatory dysfunction, n (%)	23 (40.4)	17 (37.8)	0.477

Continued

Table 1 Baseline Demographic and Principal Autonomic Data of Patients With iRBD and Controls *(continued)*

Demographics	iRBD (n = 64)	HC (n = 67)	*p* Value
SF: Sexual dysfunction, n (%)	29 (50.9)	18 (40.0)	0.186
No. of affected domains, median (IQR)	4 (4 to 6)	3 (2 to 5)	0.001
Questionnaires	iRBD (n = 57)	HC (n = 64)	
SCOPA-AUT (score), median (IQR)	9 (7 to 14)	6 (3 to 8)	0.001
COMPASS-31 (score), median (IQR)	19.67 (7.49 to 32.62)	7.90 (1.80 to 23.94)	0.009

Abbreviations: BMI = body mass index; COMPASS-31 = Composite Autonomic Symptom Score-31; CV = cardiovascular domain; DBP = diastolic blood pressure; GI = gastrointestinal domain; HC = healthy controls; HR = heart rate; IQR = interquartile range (first quartile–third quartile); iRBD = patients with isolated REM sleep behavior disorder; nOH = neurogenic orthostatic hypotension; PM = pupillary motility domain; SBP = systolic blood pressure; SCOPA-AUT = Scale for Outcomes in Parkinson's disease for Autonomic symptoms; SF = sexual function domain; TR = thermoregulatory domain; UR = urinary domain; VR = Valsalva ratio; Δ = change in value from supine resting to presented condition.
[a] Calculated excluding patients where HR could not be correctly assessed throughout the whole battery (iRBD = 54).

Baseline CRT Results

At HUTT, iRBDs exhibited slightly elevated SBP compared with HC (p = 0.006). Twelve (18.2%) iRBDs and no HC showed OH, only 1 patient was symptomatic during HUTT. In 9 of 12 iRBDs, OH was nOH (p = 0.001), in the remaining 3 HR impairment (due to atrial fibrillation or bi-trigeminism) prevented CRT interpretation.

Irrespective of the OH presence, all iRBDs showed during HUTT, compared with the supine position, a decrease in SBP and DBP (negative difference, Δ) both at the third and tenth minutes (ΔSBP 3 minutes −9.36 ± 15.31, ΔDBP 3 minutes −0.95 ± 6.33, ΔSBP 10 minutes −9.61 ± 18.07 and ΔDBP 10 minutes −1.05 ± 6.87 mm Hg; $p < 0.001$); ΔHR was significantly lower in iRBD at third minute, but not different with HCs at tenth minute (p = 0.034 and p = 0.550) (Table 1).

During VM, 27 (50.0%) iRBDs exhibited pathologic overshoot; 20 (37.0%) pathologic ΔSBP (IIb-IIa), which are signs of adrenergic autonomic failure (19%–35.2% both overshoot and ΔSBP [IIb-IIa]; eFigure 1); and 15 (27.8%) abnormal VR, underlining cardiovagal autonomic failure (11%–20.4% both overshoot and VR). All BP responses were more frequently pathologic in iRBDs than controls, whereas HR responses seemed either delayed or reduced to a lesser extent (Table 1 and eTable 2).

HG, also measuring cardiovascular adrenergic function, was more frequently abnormal in iRBDs (25.4% vs 10.6%, p = 0.026), showing attenuated BP responses (p = 0.002 and 0.021) but maintained HR changes. Similarly, DB, evaluating cardiovagal parasympathetic activity, showed differences between iRBDs and HCs in some of the metrics (eTable 3).

Twenty-five iRBDs with autonomic failure underwent ^{123}I-MIBG-SPECT, all showing reduced heart-to-mediastinum ratio except one, who later converted to MSA.

Questionnaires and Symptoms of Autonomic Impairment

Patients with iRBD exhibited higher frequencies of gastrointestinal symptoms such as mild dysphagia (22.8% vs 6.7%, p = 0.023) and constipation (31.6% vs 8.9%, p = 0.005) compared with HCs, the same was for orthostatic intolerance (61.4% vs 28.9%, p = 0.001) and pupillary dysfunction (35.1% vs 13.3%, p = 0.010). The median number of affected domains was higher in iRBDs than in HCs (4 [4–6] vs 3 [2–5]; p = 0.001). SCOPA-AUT and COMPASS-31 scores were significantly higher in iRBDs compared with HC (p = 0.001 and p = 0.009) (Table 1).

Longitudinal Evaluation

Longitudinal Demographic Data

Forty-four iRBDs had at least 1 follow-up with complete CRTs (31 men, 70%), repeated every year, resulting in an overall mean instrumental follow-up time of 2.64 ± 1.45 years (range 1.0–6.8 years), for a total of 137 evaluations (median 3, IQR 2–4, range 2–6 evaluations per patient) (Figure 1).

Longitudinal CRT Results

At longitudinal evaluations iRBDs showed a yearly decrease of ΔSBP at HUTT, both at third and tenth minutes (p = 0.034 and 0.045), consistent with an annual OR increase of nOH of 2.44 (p = 0.001) (Table 2 and eTable 4 for analyses in the subgroup of iRBDs who performed all assessments). In total, 7 more patients developed nOH during the follow-ups (total number of iRBD with nOH = 16), of them 5 already presented a pathologic VM at baseline and 2 also a delayed OH.

Longitudinal data on VM were available for 38 patients. The prevalence of pathologic VM did not change through the years, although the prevalence of an absent late phase II BP response increased (p = 0.008). iRBD also showed a decrease of VR (p = 0.015; Table 2) and a further delay of VM phase IV (p = 0.003; eTable 5).

Table 2 Longitudinal Model Coefficients for Demographic and Principal Autonomic Data Yearly Change in Patients With iRBD

Demographics	Longitudinal model β Coefficient; OR for yearly progression (95% CI)	*p* Value
BMI, kg/m^2	−0.19 (−0.40 to 0.01)	0.063
Head-up tilt test		
SBP supine resting, mm Hg	1.64 (−0.68 to 3.97)	0.166
DBP supine resting, mm Hg	−0.04 (−1.10 to 1.18)	0.939
HR supine resting, bpm	−0.24 (−0.92 to 0.44)	0.485
ΔSBP 3 min, mm Hg	−1.52 (−2.93 to −0.12)	0.034
ΔDBP 3 min, mm Hg	−0.41 (−1.00 to 0.08)	0.071
ΔHR 3 min, bpm	0.37 (−0.13 to 0.86)	0.152
nOH	2.44 (1.43 to 4.20)	0.001
ΔHR/ΔSBP ratio, bpm/mm Hg	−0.08 (−0.22 to 0.05)	0.226
ΔSBP 10 min, mm Hg	−1.99 (−3.94 to −0.05)	0.045
ΔDBP 10 min, mm Hg	−0.55 (−1.16 to 0.04)	0.061
ΔHR 10 min, bpm	0.51 (−0.09 to 0.98)	0.083
Valsalva maneuver		
Overshoot, mm Hg	−1.00 (−2.13 to 0.13)	0.072
Pathologic overshoot	0.98 (0.54 to 1.42)	0.918
VR	−0.008 (−0.019 to −0.004)	0.015
Pathologic VR	1.25 (0.82 to 1.94)	0.296
Symptoms of autonomic impairment		
CV		
Orthostatic intolerance	0.75 (0.40 to 1.41)	0.368
Syncope in past 6 mo	1.43 (0.60 to 3.40)	0.417
GI		
Mild dysphagia	1.31 (0.67 to 2.60)	0.426
Constipation	1.18 (0.81 to 1.70)	0.388
Sialorrhea	1.61 (1.00 to 2.60)	0.051
UR		
Nocturia	1.00 (0.59 to 1.68)	0.997
Urinary urgency	1.50 (0.96 to 2.35)	0.075
Urinary incontinence	1.74 (1.18 to 2.55)	0.005
PM: Pupillary dysfunction	2.13 (1.35 to 3.56)	0.001
TR: Thermoregulatory dysfunction	2.51 (1.32 to 4.75)	0.005
SF: Sexual dysfunction	1.00 (0.69 to 1.45)	0.989
No. of affected domains	0.28 (0.11 to 0.44)	0.001
Questionnaires		
SCOPA-AUT (score)	0.84 (0.22 to 1.45)	0.008
COMPASS-31 (score)	0.41 (−1.13 to 1.95)	0.602

Abbreviations: β Coefficient = longitudinal regression model yearly β coefficient; BMI = body mass index; COMPASS-31 = Composite Autonomic Symptom Score-31; CV = cardiovascular domain; DBP = diastolic blood pressure; GI = gastrointestinal domain; HR = heart rate; nOH = neurogenic orthostatic hypotension; OR = annual odds ratio; PM = pupillary motility domain; SBP = systolic blood pressure; SCOPA-AUT = Scale for Outcomes in Parkinson's disease for Autonomic symptoms; SF = sexual function domain; TR = thermoregulatory domain; UR = urinary domain; VR = Valsalva ratio; Δ = change in value from supine resting to presented condition.

Handgrip SBP and DBP responses further decreased with significant annual rates ($p = 0.004$ and $p = 0.043$ respectively). The DB test showed a reduction of HR change ($p = 0.017$) (eTable 6).

Longitudinal Questionnaires and Symptoms of Autonomic Impairment

Regarding autonomic symptoms, increased OR for yearly progression were noted for urinary incontinence (OR 1.74, $p = 0.005$), thermoregulatory dysfunction (OR 2.51, $p = 0.005$), and pupillary dysfunction (OR 2.13, $p = 0.001$), sialorrhea and urinary urgency did not reach significance. The SCOPA-AUT questionnaire demonstrated a 0.84 points yearly increase ($p = 0.008$), while COMPASS-31 scores did not show a significant change (Table 2).

Conversion and Survival Evaluation

Demographic Data and CRT Results of Converted and Nonconverted Patients

All patients were clinically followed for a mean of 4.08 ± 2.33 years (range 0.7–8.8 years), 13 (20.3%) phenoconverted to an α-synucleinopathy: 5 (38.5%) PD, 5 (38.5%) DLB, 1 (7.6%) MSA, and 2 (15.4%) undefined atypical parkinsonism. Age at iRBD onset was similar in converters (Conv) and nonconverters (non-Conv) (62.73 ± 7.50 vs 62.71 ± 7.10 years, $p = 0.994$), with no differences in age at baseline or disease duration ($p = 0.277$ and 0.610).

Conv showed higher rates of nOH during baseline HUTT compared with non-Conv (45.5% vs 9.1%, $p = 0.011$); nOH also appeared earlier in Conv during the disease course (5 [2–9.5] vs 9.5 [5–15.5] years; $p = 0.071$), though without statistical significance (eFigure 2). Significant differences were observed in BP changes during HUTT, with Conv exhibiting lower ΔSBP and ΔDBP at third and tenth minutes (Table 3 and eTable 7 for iRBDs with complete assessments).

Table 3 Baseline Demographic and Main Autonomic Data of Converted and Nonconverted Patients With iRBD

Demographics	Conv (n = 13)	Non-Conv (n = 51)	*p* Value
Sex, n (%)			
Male	11 (84.6)	37 (72.5)	0.306
Female	2 (15.4)	14 (27.5)	
Age at baseline, y, mean ± SD	70.24 ± 5.02	68.58 ± 7.10	0.277
Age at onset, y, mean ± SD	62.73 ± 7.50	62.71 ± 7.90	0.743
Duration RBD T0, y, median (IQR)	4.60 (2.60 to 12.14)	4.63 (2.86 to 9.11)	0.610
Baseline to conversion, y, median (IQR)	2.72 (1.01 to 4.13)	—	—
Head-up tilt test	Conv (n = 12)	Non-Conv (n = 49)	
SBP supine resting, mm Hg, mean ± SD	144.64 ± 20.80	139.92 ± 20.82	0.349
DBP supine resting, mm Hg, mean ± SD	71.91 ± 10.38	70.44 ± 7.58	0.753
HR supine resting, bpm, mean ± SD[a]	62.30 ± 8.1	61.76 ± 9.77	0.706
ΔSBP 3 min, mm Hg, mean ± SD	−21.36 ± 21.66	−6.72 ± 12.32	0.016
ΔDBP 3 min, mm Hg, mean ± SD	−4.00 ± 7.77	−0.28 ± 5.84	0.070
ΔHR 3 min, bpm, mean ± SD[a]	8.90 ± 4.86	6.42 ± 5.47	0.230
nOH, n (%)[a]	5 (45.5)	4 (9.1)	0.011
ΔHR/ΔSBP ratio, bpm/mm Hg, median (IQR)[a]	0.54 (0.24 to 1.50)	0.83 (0.40 to 1.60)	0.233
ΔSBP 10 min, mm Hg, mean ± SD	−26.27 ± 23.62	−5.94 ± 14.49	0.002
ΔDBP 10 min, mm Hg, mean ± SD	−4.91 ± 8.68	2.36 ± 5.72	0.004
ΔHR 10 min, bpm, mean ± SD[a]	8.00 ± 6.91	7.80 ± 6.14	0.881
Valsalva maneuver	Conv (n = 11)	Non-Conv (n = 43)	
Overshoot, mm Hg, median (IQR)	0.50 (−13.25 to 11.25)	15.50 (−6.50 to 24.75)	0.044
Pathologic overshoot, n (%)	9 (81.8)	18 (41.9)	0.020
VR, median (IQR)	1.30 (1.15 to 1.41)	1.31 (1.24 to 1.43)	0.426
Pathologic VR, n (%)	3 (27.3)	12 (27.9)	0.642
Symptoms of autonomic impairment	Conv (n = 10)	Non-Conv (n = 47)	
CV			
Orthostatic intolerance, n (%)	8 (80.0)	27 (54.7)	0.166
Syncope in past 6 mo, n (%)	3 (6.4)	0 (0.0)	0.611
GI			
Mild dysphagia, n (%)	1 (10.0)	12 (25.5)	0.271
Constipation, n (%)	5 (50.0)	13 (27.7)	0.157
Sialorrhea, n (%)	0 (0.0)	5 (10.6)	0.366
UR			
Nocturia, n (%)	8 (80.0)	29 (61.7)	0.236
Urinary urgency, n (%)	1 (10.0)	20 (42.6)	0.053
Urinary incontinence, n (%)	1 (10.0)	11 (23.4)	0.320
PM: Pupillary dysfunction, n (%)	2 (20.0)	18 (38.3)	0.236
TR: Thermoregulatory dysfunction, n (%)	1 (10.0)	22 (46.8)	0.031

Continued

Table 3 Baseline Demographic and Main Autonomic Data of Converted and Nonconverted Patients With iRBD *(continued)*

Demographics	Conv (n = 13)	Non-Conv (n = 51)	*p* Value
SF: Sexual dysfunction, n (%)	5 (50.0)	24 (51.1)	0.951
No. of affected domains, median (IQR)	3 (2 to 4)	4 (2 to 4)	0.674
Questionnaires	Conv (n = 10)	Non-Conv (n = 47)	
SCOPA-AUT (score), median (IQR)	9.5 (6 to 12)	9 (7 to 16)	0.690
COMPASS-31 (score), median (IQR)	26.98 (21.87 to 36.00)	17.33 (6.29 to 32.62)	0.140

Abbreviations: COMPASS-31 = Composite Autonomic Symptom Score-31; Conv = patients with iRBD converted to an overt α-synucleinopathy; CV = cardiovascular domain; DBP = diastolic blood pressure; GI = gastrointestinal domain; HR = heart rate; IQR = interquartile range (first quartile–third quartile); nOH = neurogenic orthostatic hypotension; non-Conv = patients remained isolated; PM = pupillary motility domain; SBP = systolic blood pressure; SCOPA-AUT = Scale for Outcomes in Parkinson's disease for Autonomic symptoms; SF = sexual function domain; TR = thermoregulatory domain; UR = urinary domain; VR = Valsalva ratio; Δ = change in value from supine resting to presented condition.
[a] Calculated excluding patients where HR could not be correctly assessed throughout the whole battery (Conv = 11; non-Conv = 43).

VM results indicated more pronounced abnormalities in Conv, with lower median overshoot (Conv = 0.50 [−13.25 to 11.25] vs non-Conv = 15.50 [−6.50 to 24.75] mm Hg; $p = 0.044$), which was also more frequently abnormal (81.8% vs 41.9%, $p = 0.020$) (Table 3 and eTable 8). HG showed lower ΔSBP and ΔDBP in Conv (18.55 ± 15.58 vs 32.92 ± 15.90 and 9.91 ± 6.22 vs 17.27 ± 7.30 mm Hg; $p = 0.013$ and $p = 0.004$), while DB showed reduced HR change (6.0 [5.0–10.0] vs 9.0 [5.5–12.0] bpm) and was partially more abnormal in Conv (eTable 9).

Symptoms of autonomic impairment generally failed to differentiate Conv from non-Conv; however, thermoregulatory symptoms were more frequent in non-Conv ($p = 0.031$). Moreover, when considering the subscores of SCOPA-AUT and COMPASS-31, both cardiovascular domain and orthostatic intolerance subscores were higher in Conv (2.50 [0.75–3.25] vs 1 [0–2] and 18 [16–22] vs 12 [0–16]; $p = 0.025$ for both). The latency of autonomic symptom onset did not differ between the 2 groups (eFigure 2).

Survival Evaluation

At conversion, the mean age was 73.01 ± 5.16 years and the median disease duration 6.32 (4.25–12.40) years. Kaplan-Meier estimate of phenoconversion in the overall cohort is shown in Figure 2A. Among the significant parameters differentiating Conv and non-Conv and general variables of interest, univariate Cox regression analyses identified nOH (HR 5.05; 95% CI 1.39–18.38; $p = 0.012$), pathologic VM (<10 mm Hg), and pathologic I/E ratio at DB (<1.10) as nominal factors associated with conversion (Table 4 and eTable 10 for iRBDs with complete assessments). This association was confirmed by Kaplan-Meier analysis curves for nOH and DB (Figure 2, B and D), below significance for VM overshoot (Figure 2C). Early presentation of these conditions (<5 years from the onset of iRBD) further increased the risk (Table 4, eFigures 3 and 4).

Nonetheless, the reduction of BP responses at HUTT and HG were also continuous factors of higher risk of conversion (Table 4).

The small number of Conv and of patients in whom we were able to define the presence or absence of nominal variables did not allow multivariable Cox proportional analysis.

Discussion

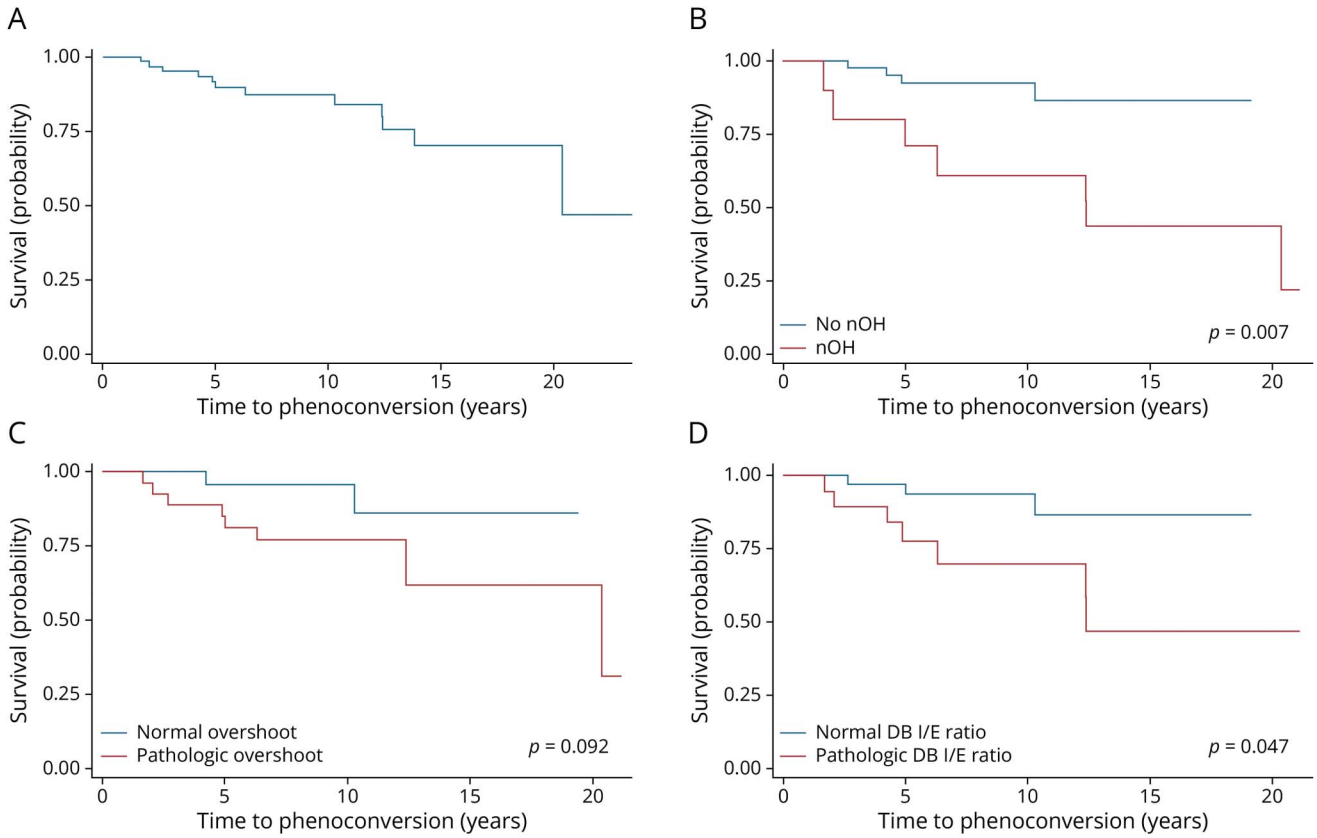
We reported a large cohort of iRBD patients with longitudinal comprehensive objective evaluation of cardiovascular autonomic function and symptoms of autonomic impairment. Our results confirmed that symptoms of autonomic impairment are more prevalent in patients with iRBD (especially constipation and orthostatic intolerance) (state marker) and may progress over time (monitoring marker). However, only cardiovascular autonomic failure was confirmed as a true multidimensional marker as (1) cardiovascular autonomic failure is present in up to half of iRBD (state marker); (2) shows a yearly deterioration (monitoring marker); and (3) several objective variables of cardiovascular autonomic failure seem as factors increasing the risk of phenoconversion (prognostic marker).

Considering autonomic failure as a state marker, we showed a global impairment of cardiovascular autonomic control in patients with iRBD, with a more marked alteration of the sympathetic (adrenergic) component.

A recent article,[13] evaluating OH with 3-minute orthostatic stand testing and autonomic questionnaires in 340 iRBDs from the North American Prodromal Synucleinopathy cohort, found a 27% prevalence of OH (21% for nOH). Our lower prevalence (19.7% OH; 16.7% nOH) may be explained by the different methods for the OH assessment (65° HUTT vs standing), and the definition of its neurogenic origin (pathologic VM vs ΔHR/ΔSBP ratio <0.5[25]), by the selection of a MDS-UPDRSIII cutoff value to exclude motor impairment, and by the withdrawal of cardiovascular-active drugs before CRTs.

The sympathetic alteration was supported by more frequently abnormal BP responses to HUTT, with less

Figure 2 Kaplan-Meier Survival Curves for Probability of Phenoconversion From iRBD Onset



(A) Survival analysis from disease onset to phenoconversion to an overt α-synucleinopathy in all patients with iRBD. (B) Survival analysis in those with neurogenic orthostatic hypotension (nOH) and those without (No nOH). (C) Survival analysis in those with pathologic and normal overshoot at Valsalva maneuver. (D) Survival analysis in those with pathologic and normal I/E ratio (ratio between the average of the 10 shortest RR intervals in inspiration and in expiration) at the deep breathing test (DB I/E ratio). iRBD = isolated REM sleep behavior disorder.

impaired HR changes (especially during the late tilt). This is in line with what reported in studies with smaller cohorts, evaluating BP by means of beat-to-beat monitoring during CRT.[29-31] Further data in favor of a sympathetic alteration of the baroreflex arc and of vasomotor efferences[22] were brought by the reduced or absent overshoot at VM, found in 50% of iRBDs, and by the higher prevalence of abnormal HG, respectively.

The baroreflex response of tachycardia to upright posture is biphasic because it depends on parasympathetic cardiovagal withdrawal, stabilized by sympathetic stimulation,[32] as was postulated for cardiac baroreflex gain (i.e., ΔHR/ΔSBP ratio).[25] Sinus arrhythmia response at DB and VR test the efferent cardiovagal function, while the latter is dependent from the BP response.[33,34] Our patients showed reduced, but within normal, HR responses at the third minute of HUTT, which became nondifferent to controls at the tenth minute, suggesting the loss of only a part of the HR response. Moreover, not only ΔHR/ΔSBP ratio was comparable with HC, but its validated cutoff of <0.5 failed to identify 1 patient with nOH. VR was reduced compared to HC, while indices of HR response at DB did not show differences in all metrics. Thus, we may postulate that patients with iRBD show a less impaired cardiovagal function, accounting for the partially conserved HR responses, thus a lesser involvement of the parasympathetic branch of ANS.[35,36] To note, a patient with baroreflex-sympathoneural failure, recently described by Goldstein and collaborators, showed CRT results similar to the trend of our patients with iRBD.[37]

When considering OH symptoms, in our patients, the prominent cardiovascular autonomic alteration was in line with the higher prevalence of orthostatic intolerance.

In α-synucleinopathies, distinguishing peripheral (typical in PD) from central (MSA) autonomic failure is crucial. Previous hypotheses proposed a peripheral origin of ANS impairment in iRBD, akin to PD.[10,11] However, some patients, more frequently with preserved cardiac sympathetic innervation, convert to MSA[27] and studies using advanced imaging revealed central ANS alterations in iRBD.[8,38] Our data cannot distinguish the central or peripheral origin of autonomic failure. On one hand, the high proportion of abnormal cardiac ^{123}MIBG-SPECT indicates a peripheral

Table 4 Variables Associated With Conversion to Overt Synucleinopathies in the Univariate Cox Regression Analysis

		Cox regression analysis	
Demographics	**n**	**Unadjusted hazard ratio (95% CI)**	***p* Value**
Age at onset	64	0.94 (0.80 to 1.10)	0.415
Sex			
Male	48	1 (reference)	—
Female	16	0.57 (0.16 to 2.02)	0.381
Head-up tilt test			
10 mm Hg decrease of ΔSBP 3 min	61	1.34 (1.00 to 1.79)	0.052
nOH and history of orthostatic intolerance	12	3.02 (0.95 to 9.28)	0.053
nOH	16	5.05 (1.39 to 18.38)	0.012
Early nOH	6	15.63 (3.46 to 70.49)	<0.001
20 mm Hg decrease of ΔSBP 10 min	61	1.76 (1.17 to 2.66)	0.007
10 mm Hg decrease of ΔSBP 10 min	61	1.33 (1.08 to 1.63)	0.007
10 mm Hg decrease of ΔDBP 10 min	61	1.89 (0.95 to 3.78)	0.071
Valsalva maneuver			
1 mm Hg decrease of overshoot	54	1.02 (0.99 to 1.04)	0.237
Pathologic overshoot	29	3.49 (0.86 to 16.14)	0.099
Early pathologic overshoot	14	16.05 (2.22 to 115.92)	0.006
Handgrip			
10 mm Hg decrease of ΔSBP	59	1.29 (0.97 to 1.70)	0.080
10 mm Hg decrease of ΔDBP	59	1.58 (0.81 to 3.08)	0.183
Pathologic HG	23	2.38 (0.71 to 7.98)	0.161
Deep breathing			
1 bpm decrease of ΔHR	54	1.14 (0.95 to 1.37)	0.173
Pathologic DB ΔHR	29	2.18 (0.63 to 7.55)	0.218
1 unit decrease of HR I/E ratio	54	5,369.82 (0.17 to 1.72 × 10^8)	0.105
Pathologic DB I/E ratio	26	3.27 (0.95 to 11.29)	0.060
Early pathologic DB I/E ratio	14	10.52 (2.19 to 50.47)	0.003
Pathologic DB (number, %)	29	2.18 (0.63 to 7.55)	0.218
Early pathologic DB	14	9.03 (1.95 to 41.70)	0.005
Symptoms of autonomic impairment			
Urinary urgency	14	1.85 (0.53 to 6.47)	0.333
Thermoregulatory dysfunction	19	2.83 (0.73 to 11.07)	0.134

Abbreviations: DB = deep breathing test; DBP = diastolic blood pressure; Early = condition developed <5 years from iRBD onset; HG = handgrip test/maneuver; HR = heart rate; I/E ratio = ratio between the average of the 10 shortest RR intervals in inspiration and in expiration; n = number of patients with available data or with that condition (throughout the follow-ups); nOH = neurogenic orthostatic hypotension; SBP = systolic blood pressure; Δ = change in value from supine resting to presented condition.

involvement, on the other, we cannot exclude the central origin, given that iRBD already implies neurodegeneration of brainstem nuclei.

Among other autonomic symptoms, often evaluated from questionnaire data, gastrointestinal motility dysfunction has always been shown as one of the most important alterations

in iRBDs,[35,39] as confirmed also by our data, while urinary, the second most affected domain in the literature did not show prominent differences with controls, though presenting similar prevalence and scores.[13,31,39] The presence of many of these symptoms in the elderly population may limit their specificity in these patients.[40]

Over follow-ups, patients with iRBD exhibited a progressive decline in sympathetic function, with decreasing BP responses to test stimuli, exemplified by the increase of nOH, with a yearly OR of 2.44. However, some sympathetic tests such as HG did not show an increased prevalence of abnormalities, possibly due to the relatively short follow-up duration (2.64 ± 1.45 years) or to a floor effect (blunted responses at baseline). Longitudinal HR responses, especially VR, sinus arrhythmia during the DB test, and an increased prevalence of ΔHR/ΔSBP ratio <0.5 at HUTT, indicated further cardiovagal deterioration. Symptoms of autonomic failure, reflected in increased SCOPA-AUT scores, worsened yearly, though not for orthostatic intolerance, aligning with the only other finding showing an aggravating trend in symptoms from diagnosis.[41]

Limited longitudinal data on CRTs in iRBD exist, with 1 small cohort showing decreased BP response at HUTT and VM over approximately 3.5 years.[42] Other studies evaluating orthostatic SBP change[43] or 24-hour BP monitoring[44] failed to capture changes over comparable or longer follow-up periods. Recently, quantitative nuclear medicine techniques revealed worsening cardiac sympathetic degeneration after 3 years.[45] This suggests a slow deterioration over time of ANS, aligning with the evidence of OH emerging up to 15 years before conversion to a synucleinopathy.[43] In conclusion, we provided valuable insights into the progressive ANS deterioration of iRBD, highlighting the need for thorough evaluation and larger cohorts to understand the gradual yet relentless deterioration over time.

In our cohort, 13 patients (20.3%) converted to an α-synucleinopathy over the ∼4 years of follow-up. Neurogenic OH, altered sympathoneural baroreflex function (altered BP responses at HUTT and VM overshoot), and blunted cardiovagal responses (especially at DB test) not only were more frequent in Conv but were also significant risk factors for phenoconversion. When nOH, reduced VM overshoot and altered DB tests were found within 5 years from RBD onset, the risk further increased, up to 4-fold. On the contrary, neither orthostatic intolerance nor other symptoms of autonomic failure were sufficiently strong to increase the likelihood of phenoconversion, and the latency of their presentation did not differ between Conv and non-Conv. Only thermoregulatory dysfunction was more common in non-Conv than Conv at baseline, although Cox regression analysis did not yield a significant hazard ratio.

Symptoms of autonomic failure showed inconstant strength as risk factors in different, even multicenter studies,[1,39,46] probably for their subjective nature. Only constipation, which finds its origin in the alteration of the brain-gut axis, with involvement of the enteric nervous system,[47] kept a sufficient significance at a recent metanalysis.[48] Given the variability inherent in patient-reported outcomes, these findings should be interpreted with caution.

On the other hand, objective evaluations of ANS as risk markers for conversion are scarce; in iRBD, evidence is present only for OH,[43,46,48] with variable solidity. Thorough evaluations are found only in a retrospective study showing greater cardiovagal alterations at composite autonomic severity score in DLB converters relative to PD[12] and in at-risk cohorts with no vPSG diagnosis of RBD, where nOH, sympathetic alterations of the baroreflex and reduced cardiac ^{18}F-dopamine PET uptake were more frequent in central DLB converters.[14,49] Although our data suggest cardiovascular autonomic impairment as a risk factor for phenoconversion, more evidence is needed to distinguish the trajectories for different α-synucleinopathies.

The small number of Conv and the relatively short follow-up did not allow, in our study, to perform multivariate conversion modelling and to explore pathways for conversion to a specific disease. Furthermore, as OH was mostly asymptomatic, its onset may have been underestimated because it may have happened for RBD, an issue affecting all the studies with these patients. ^{123}I-MIBG-SPECT imaging was not available for all patients, which prevented further implications on the peripheral-central origin of the dysfunction. Finally, although cardiovascular autonomic failure was the main focus of this work, our study lacked objective data on other autonomic domains.

On the other hand, our study presented its strengths in the objective, repeated longitudinal evaluations of cardiovascular ANS control, which in a prospective setting allowed to delineate trajectories of ANS dysfunction in iRBD. Moreover, the stringent inclusion criteria allowed us to select real isolated patients, preventing overrepresentation of abnormalities in patients already showing prominent signs of conversion.

Autonomic failure and RBD go hand-in-hand toward α-synucleinopathies and the presence of both increases the burden of neurodegeneration. We previously demonstrated that RBD and its early appearance affect not only the clinical picture but also the phenoconversion of the peripheral iAF[4] and the development of the central MSA[50]; now, though the mixed central-peripheral origin of the process, we may be looking at the other side of the coin, retracing the steps of synuclein-related neurodegeneration. Moreover, the appearance of cardiovascular autonomic failure in the earlier years may reveal a more malignant process from the start, and its development or worsening a proximity to conversion.

This may lead to important implications, not only for including objective evaluation of autonomic impairment in the

clinical workup of patients with iRBD, but also to turn on the attention on these patients with incident or earlier involvement of more systems.

Cardiovascular autonomic failure has what it takes to represent a multimodal marker to evaluate the staging, the progression of the neurodegeneration, and the risk for conversion. These are the prerequisites that highlight the need to delineate precise disease trajectories to define the "when," but also the "where" of phenoconversion. Studies need to be accurate and precise, but also robust from a numerosity perspective, by increasing the cohort number and prolonging the time of follow-up.

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Author Contributions

L. Baldelli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. L. Sambati: major role in the acquisition of data; analysis or interpretation of data. F. Di Laudo: major role in the acquisition of data. P. Guaraldi: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G. Giannini: analysis or interpretation of data. A. Cecere: major role in the acquisition of data. G. Loddo: major role in the acquisition of data. G. Mainieri: major role in the acquisition of data. F. Mignani: major role in the acquisition of data. G. Barletta: major role in the acquisition of data; analysis or interpretation of data. P. Cortelli: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. F. Provini: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. G. Calandra-Buonaura: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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