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Exploring the Electrocardiogram as a Potential Tool to Screen for Premotor Parkinson's Disease

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Abstract: The aim of this study was to test the hypothesis that patients with REM sleep behavior disorder, many of whom will develop Parkinson's disease (PD) or a related synucleinopathy, will demonstrate decreased heart rate variability (HRV) compared with a group of age-matched controls as measured by an electrocardiogram during wakefulness. We compared HRV in 11 untreated idiopathic REM sleep behavior disorder patients (9 men and 2 women; mean age, 63.3 years; SD, 7.5 years) and 11 control subjects with idiopathic insomnia without REM sleep behavior disorder (7 men and 4 women; mean age, 59.5 years; SD, 8.7 years). Subjects with other causes of reduced HRV were excluded. HRV was determined from 5-minute presleep segments of a single channel electrocardiogram recorded during polysomnographic evaluations, using R-R intervals during wakefulness. Time domain, geometric measures, and spectral analysis of the R-R intervals were significantly different between cases and controls. A discriminant function analysis correctly classified 95.5% of subjects (overall model fit, $P = 0.016$). Leave-one-out cross-validation correctly classified 77.3% of subjects. HRV during wakefulness is significantly decreased in patients with idiopathic REM sleep behavior disorder compared with control subjects, suggesting abnormalities of both sympathetic and parasympathetic function. Patients with RBD may later develop motor and cognitive features of a Lewy body disorder, such as PD. Cardiac autonomic dysfunction is also impaired in PD, suggesting that impaired HRV may be an early sign of PD. HRV measured by routine electrocardiograms could be used to screen for Lewy body disorders such as PD. © 2010 Movement Disorder Society

Key words: heart rate variability; electrocardiogram; cardiac autonomic dysfunction; Parkinson's disease; pre-motor Parkinson's disease.

There is increasing evidence that Parkinson's disease (PD) is a widespread disorder of brain, spinal cord, and peripheral autonomic nervous system.[1–3] Although there is still much to learn about the pattern of disease origin and evolution, it is very clear that many of the signs and symptoms associated with the disorder can precede the typical motor symptoms of PD, sometimes by many years. Indeed, the work of Braak et al[4] suggests that involvement of the dopaminergic substantia nigra, which underlies the primary motor features of the disease, occurs at a time when the disorder is well advanced at a neuropathologic level, an observation that may account for the lack of success in identifying disease-modifying agents. For these reasons, there is increasing interest in identifying premotor or prodromal signs and symptoms of PD to identify the disorder in its earliest stages, well before motor symptoms are evident. Ideally, any such approach should be amenable for screening the general population.

The current study investigated electrocardiographic (EKG) assessment of cardiac autonomic dysfunction

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(CAD) as one path to achieve this goal. CAD is a near-universal feature in PD when motor signs are manifest,[5–7] and several lines of evidence suggest it may precede the motor features. For example, Lewy bodies have been observed in the superior sympathetic ganglia, which innervate the heart, many years before the clinical manifestations of PD.[8] Furthermore, Lewy neurites have been reported in the extrinsic and intrinsic nerve fibers that innervate the heart in incidental Lewy body cases, a condition thought by many to be early, premotor PD.[9] One physiologic consequence of cardiac autonomic denervation is reduction of heart rate variability (HRV), a well-documented phenomenon in patients with clinically diagnosed PD.[10,11] HRV can easily be assessed using a standard EKG and, thus, potentially represents a near-universally available noninvasive method of measuring cardiac autonomic denervation.[12]

Based on these observations, we hypothesized that patients with premotor PD (including CAD) likely will have decreased HRV as measured by a standard waking EKG. To test this hypothesis, we turned to patients with idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD), a population known to be at risk for developing a Lewy Body disorder. RBD, a REM parasomnia,[13,14] has been associated with alpha-synucleinopathies[14–16] including PD, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Because up to 50% of patients with iRBD eventually develop parkinsonism,[17–20] it has been suggested that a large proportion have premotor PD.

Our long-term goal is to determine if EKG can be used as a simple, noninvasive screening tool for premotor PD that could be incorporated into routine physical examinations of individuals in their 50s and beyond. Thus, the aim of this study was to determine if EKG recordings could be used to identify HRV changes, as a marker for CAD, in this unique population of individuals with possible premotor PD. If successful, this could provide a useful screening tool for identifying cardiac autonomic denervation, as neither ^{123}I-MIBG (meta-iodobenzylguanidine) cardiac scintigraphy nor fluorodopa positron emission tomography scanning are practical for screening purposes.

METHODS

Case Subjects

Eleven subjects with idiopathic iRBD and no major medical disorders or use of medications that might affect HRV were identified by manual review of accessible records of patients who underwent polysomnography (PSG) at the Stanford Sleep Medicine Center (SSMC) (Redwood City, CA). Clinic charts and sleep recordings conducted from 2000–2008 were systematically reviewed to confirm patients met International Classification of Sleep Disorders, Second edition[21] diagnostic criteria for iRBD.

Control Subjects

Because PSGs from healthy normal controls were unavailable, PSGs from age-matched SSMC patients diagnosed with primary insomnia during the same time period were selected. Primary insomnia is not associated with neurologic disease or autonomic dysfunction, including abnormalities of HRV.[22] Similarly to the RBD group, potential control subjects with major medical disorders or those taking medications that might affect HRV were ineligible.

Data Retrieval and Analysis

All data were originally collected and stored digitally using the Sandman Elite (Embla Systems, Denver, CO, USA)®[23] sleep diagnostic system at SSMC, using identical methods in cases and controls. De-identified PSG data from subjects meeting inclusion/exclusion criteria were provided to the Parkinson's Institute for blinded HRV analysis. An EKG segment recorded after biocalibration but before the onset of sleep was identified within the first 15 minutes of the PSG recording. A 5-minute portion of the EKG under stable conditions (stable breathing and no leg movements) was visually identified during this period for each subject. Any ectopic beats were manually removed, and beat-to-beat (RR) interval data for this period were saved for further HRV analysis.

HRV Analysis Tools

The normal-to-normal (i.e., resulting from sinus node depolarization) RR interval was input to a software program developed to study HRV by the University of Kuopio, Finland.[24] This program was used to calculate all time- and frequency-domain, as well as geometric and non-linear parameters commonly used in HRV analysis.[12]

Parameters Evaluated

HRV quantification can be separated into three categories influenced by either the sympathetic or parasympathetic nervous system or as indicators of sympathovagal balance.[12,25]

Time-Domain Measures

Time-domain measures are statistics, similar to standard deviations, which describe the variability of

the RR interval. These include standard deviation of RR intervals (SDNN), standard deviation of heart rate (SDHR), root mean square difference of successive RR intervals (RMSSD), and percentage of consecutive RR intervals differing by more than 50 msec (pNN50). SDNN indicates overall HRV and is influenced by both sympathetic and parasympathetic innervation, whereas RMSSD and pNN50 are thought to be indicators of parasympathetic innervation.[12,25]

Geometric and Nonlinear Measures

The RR interval signal is highly nonlinear in nature, reflecting complex interactions between hemodynamic, electrophysiologic, and humoral variables, as well as autonomic and central nervous regulation.[12] This nonlinearity can be represented as a Poincaré plot, which portrays the relationship between consecutive RR intervals (an RR interval plotted against the preceding one). By fitting an ellipse onto the line-of-identity at 45° to the normal axis of the Poincaré plot, the standard descriptors SD1 (minor axis) and SD2 (major axis) are obtained, providing summary information about beat-to-beat (short term) and overall HRV respectively.

The RR intervals can be converted to a geometric pattern such as a sample density distribution. For example, a histogram of NN interval durations can be used to demonstrate the relationship between the total number of RR intervals detected and the RR interval variation. Mathematical formulas are then used to calculate HRV parameters on the basis of the geometric properties of the resulting pattern. The RR interval sequence is converted to a discrete scale to calculate the geometric HRV parameters, RR triangular index (RRTRI), and triangular interpolation of NN (TINN). RRTRI is given by the number of all NN intervals divided by the height of the histogram of all NN intervals. TINN is calculated based on the RR interval histogram interpolated as a triangle using the mathematical technique of minimum square differences. TINN is the baseline width of the distribution measured as a base of a triangle approximating the NN interval distribution. Both RRTRI and TINN are indicators of overall HRV, influenced by both sympathetic and parasympathetic nervous systems.[12,25]

Frequency-Domain Measures

Information regarding power (variance) distribution across frequencies in the RR interval signal is obtained using power spectral density. We used the nonparametric fast Fourier transforms technique, a commonly used mathematical approach for transforming time-dependent signals (e.g., RR intervals) to the frequency domain. Powers in the three frequency bands of HRV, very low frequency (VLF: 0–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15-0.4 Hz), and total spectral power were obtained. Absolute and normalized units (LFnu and HFnu), i.e., the relative value of each component in proportion to total power minus the VLF component,[24] were then calculated. HF is related to respiration and parasympathetically mediated. LF is influenced by both sympathetic and parasympathetic components. The LF/HF ratio may indicate sympathovagal balance. VLF likely involves thermoregulatory and peripheral vascular mechanisms.[12,25]

Statistical Analysis

Univariate HRV differences between patients with iRBD and control subjects were tested using nonparametric Mann Whitney *U* tests. Two-tailed exact *P*-values are reported. Receiver operating characteristic curves were generated for each variable to assess its ability to discriminate between cases and controls. Discriminant analysis generally provides more stable models than logistic regression for small sample sizes[26] and was used to develop multivariable classification models. Non-normal variables and variables with significant nonhomogeneous variance were natural log-transformed before inclusion in discriminant function models. Variables with tolerance values approaching zero were excluded to avoid matrix ill-conditioning due to variable redundancy. Because of the small sample size, models were cross-validated using the leave-one-out method.[27] All analyses were conducted with SPSS version 10.

RESULTS

Study Subjects

Mean age of the nine men and two women with iRBD was 63.3 years (SD, 7.5 years). One subject had a prior PSG documenting RBD and was taking clonazepam. No other subject had been diagnosed before their SSMC PSG, and none was receiving treatment for RBD. Seven men and four women with insomnia who met inclusion criteria were enrolled as controls (mean age, 59.5 years; SD, 8.7).

HRV Analysis

Time-Domain Measures

Overall HRV (SDNN; $P < 0.05$) and the parasympathetic indicator pNN50 ($P < 0.04$) were significantly reduced in patients with iRBD compared with controls.

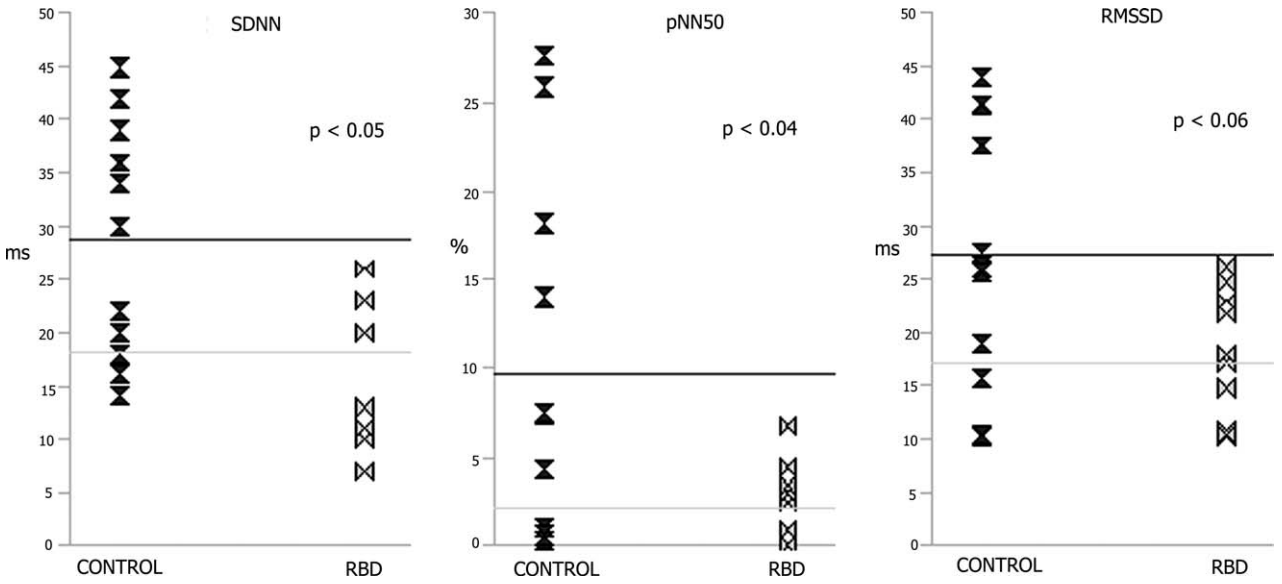

FIG. 1. Time-domain measures of HRV. HRV time-domain measures of SDNN, pNN50 and RMSSD between control subjects and patients with RBD are shown. SDNN ($P < 0.05$) and pNN50 ($P < 0.04$) were significantly less for the iRBD patients compared with control subjects. RMSSD was lower in iRBD.

RMSSD was lower in cases and tended toward significance (Fig. 1; Table 1).

Geometric and Nonlinear Measures

All measures in this category other than RRTRI were significantly lower in the iRBD group. These included SD1 ($P = 0.05$), SD2 ($P < 0.01$), and TINN ($P < 0.05$). RRTRI was also lower in cases and tended toward significance.

Frequency-Domain Analysis

LF ($P < 0.03$) and HF ($P = 0.04$) power density parameters were significantly lower in patients with iRBD. Total power density tended toward significance (Fig. 2).

Discriminant Analysis

After exclusion of variables failing the tolerance test, valid model parameters included SSDN, SDHR, RMSSD, pNN50, SD2 Poincaré, RRTRI, TINN, VLF, LF, HF, LF/

TABLE 1. *HRV parameters in case and control subjects*

Domain	Parameter	Case	Control	*P**	ROC area under curve
Time	SDNN	18.1 (6.7)	28.7 (11.2)	0.049	0.75
	SDHR	1.84 (0.78)	2.65 (1.04)	0.10	0.71
	RMSSD	17.0 (6.2)	27.1 (12.5)	0.058	0.74
	pNN50	2.13 (2.21)	9.65 (10.3)	0.038	0.76
Geometric and nonlinear	SD1	12.3 (4.5)	19.6 (9.0)	0.042	0.76
	SD2	44.5 (21.0)	68.9 (32.9)	0.009	0.82
	RRTRI	0.0386 (0.0119)	0.0517 (0.0158)	0.068	0.73
	TINN	96.4 (33.7)	150.9 (62.0)	0.045	0.75
Frequency	VLF	11.1 (8.1)	22.6 (17.7)	0.16	0.68
	LF	102 (73.0)	350 (294)	0.028	0.78
	LFnu	61.4 (17.5)	69.7 (20.0)	0.12	0.70
	HF	48.9 (31.8)	134 (112)	0.04	0.76
	HFnu	38.1 (17.0)	30.0 (19.4)	0.12	0.30
	LF/HF	2.15 (1.45)	3.30 (1.98)	0.12	0.70
	Total power	162 (103)	506 (395)	0.056	0.74

HRV domain measures in patients with iRBD (cases) and control subjects are shown. Values are given as mean (standard deviation).

*Mann-Whitney nonparametric exact *P*.

ROC, receiver operating characteristic.

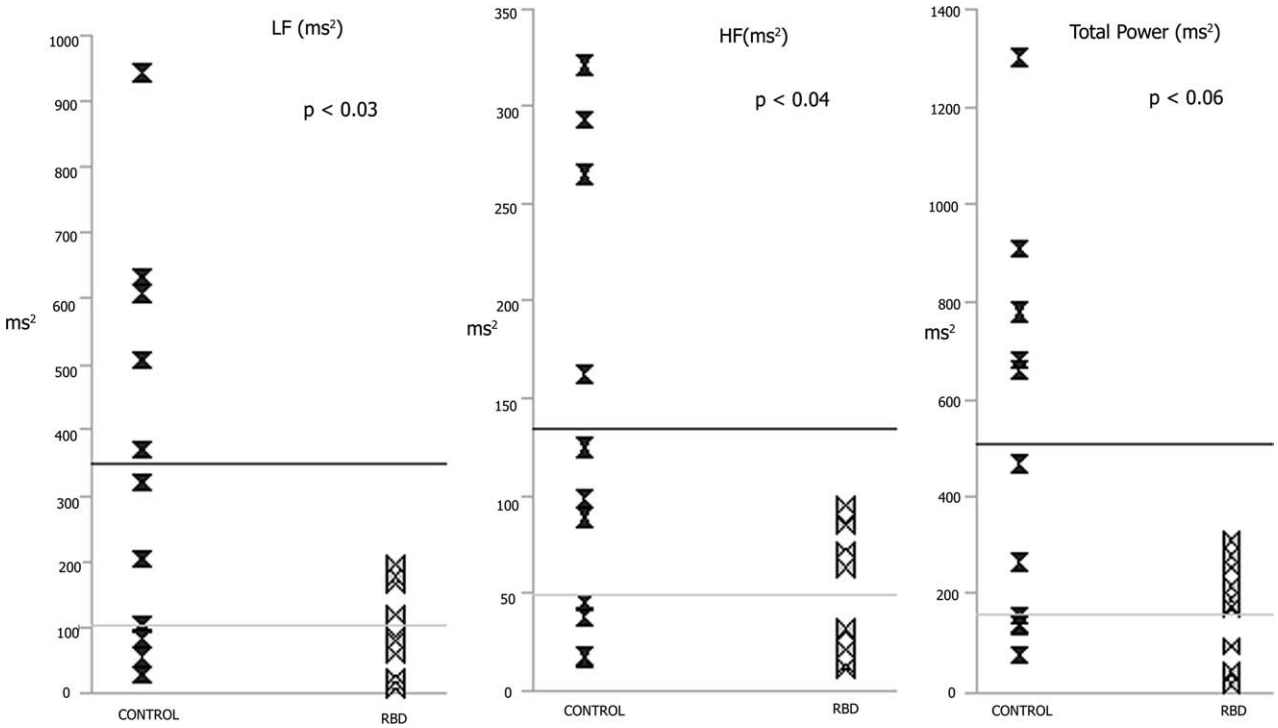

FIG. 2. Frequency-domain measures of HRV calculated using fast Fourier transform (FFT). HRV frequency-domain measures of LF (ms^2), HF (ms^2) and total power (ms^2) between control subjects and patients with iRBD are shown. LF ($P < 0.03$) and HF ($P < 0.04$) were significantly lower in iRBD vs. controls. Total spectral power was lower in the iRBD.

HF, and age. The standardized canonical discriminant function coefficients are provided in supplemental material online (Supplementary Table; Fig. 3). Overall model fit was statistically significant ($P = 0.016$) and correctly classified 95.5% of subjects. Only a single control subject was incorrectly classified. Leave-one-out cross-validation correctly classified 77.3% of subjects, misclassifying two case and three control subjects.

DISCUSSION

To the best of our knowledge, this is the first study to use detailed analysis of the EKG to examine HRV in patients with iRBD during wakefulness. We found significant reductions in all three standard measurement domains of HRV, suggesting both sympathetic and parasympathetic influences on cardiac function are decreased in patients with iRBD compared with controls. Although a number of previous studies focused on cardiac sympathetic denervation in PD, in our investigation, HRV measures thought to be primarily mediated by parasympathetic innervation were significantly attenuated as well, including pNN50, the width of Poincaré plot SD1, and HF spectral power. Overall, our results suggest an abnormality in autonomic innervation of the heart in iRBD that can be identified by a standard waking EKG. We are aware of only one prior study that assessed HRV using a waking EKG to measure the R-R interval.[13] This group observed no changes but only measured a 20-second EKG recording—far less than the generally accepted 5-minute standard required to accurately assess HRV and carry out a spectral analysis, which the authors recommended as a next step.

There is already a substantial body of literature suggesting patients with iRBD have disturbance in autonomic innervation of the heart. Lanfranchi et al[28] studied HRV during REM and non-REM sleep in 10 patients with iRBD and found that differences normally observed between REM and non-REM sleep were not present in patients with iRBD, indicating a loss of cardiac autonomic innervation. Miyamoto et al[29] used ^{123}I-MIBG cardiac scintigraphy to measure cardiac sympathetic denervation in patients with iRBD and observed reduced uptake in all 13 patients. Interestingly, these changes were similar to those observed in PD and DLB,[30] adding further evidence to the hypothesis that iRBD is part of a continuum including PD and DLB. In some,[31] but not all,[32] cases, these changes progressed over time. Unfortunately, cardiac imaging is not amenable for use as a screening procedure.

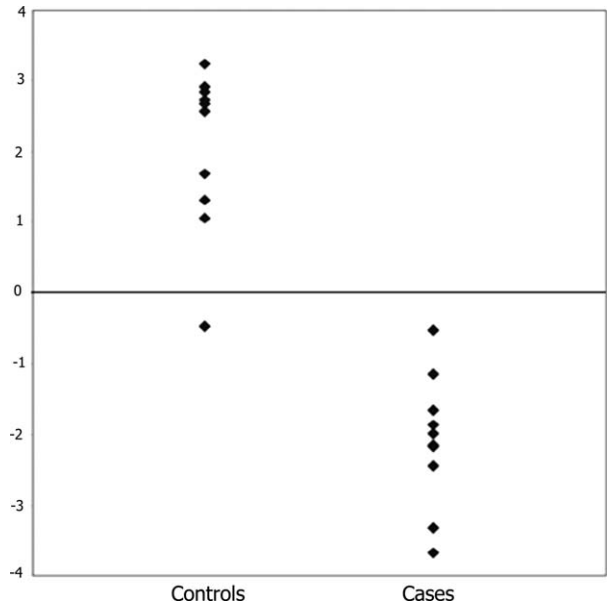

FIG. 3. Discriminant classification scores in cases and controls. Discriminant classification scores for controls and cases (iRBD) shown. Overall model fit was statistically significant ($P = 0.016$), correctly classifying 95.5% of subjects, misclassifying one control subject. Leave-one-out cross-validation correctly classified 77.3% of subjects, misclassifying 2 case and 3 control subjects.

We chose patients with iRBD as a population with possible premotor PD and/or a related synucleinopathy based on growing evidence that RBD may be an early manifestation of a chronic progressive brainstem synucleinopathy that may progress to PD or a related disorder. Schenk et al[20] first reported that patients with RBD are likely to develop PD or a related synucleinopathy if followed up long enough. More recently, Postuma et al[19] found the 5-year risk of developing neurodegenerative disease in patients with RBD was 18%, with a 12-year risk of 52%; Iranzo et al.[18] reported 45% of pure RBD developed PD or LBD at 11.5 years. Thus, a substantial portion of patients with RBD probably have an underlying degenerative disorder, which is likely a LBD such as PD. To date, there are only three reports of neuropathologic findings in pure RBD cases. Two of these manifested a pathologic picture of typical PD with alpha-synuclein positive Lewy bodies and neurites;[33,34] a third had cortical Alzheimer's disease changes and Lewy bodies, but the brainstem was not examined for Lewy bodies.[35] Lewy bodies and alpha-synuclein pathologies seem to be a common pathologic factor in iRBD.

Our results show that subjects with iRBD were significantly different from controls in several HRV parameters and could be correctly separated from controls using an exploratory discriminant function analysis. Because impaired HRV is a consequence of CAD, these findings suggest that assessment of HRV using a simple EKG may be a useful screening tool for CAD. CAD is also found in PD and may precede motor signs. This supports our idea that assessing HRV could serve as a screening test for premotor PD or a related synucleinopathy. However, there are a number of issues that need to be addressed before implementing this approach. First, these results must be considered preliminary because of the small number of subjects and selected nature of the population. Because RBD prevalence in the general population is estimated at 0.5%,[36] patients ascertained from sleep centers likely represent a selected subset. Therefore, it will be important to independently replicate these results in a larger cohort of iRBD patients and ultimately in a population-based study. Second, because this was a cross-sectional analysis of preexisting data, we relied on PSGs from insomnia patients as controls. We believe this was justified in view of a recent study,[22] indicating no differences in HRV as measured by waking EKG recordings in patients with insomnia compared with controls. Furthermore, our selection of controls from the same clinic as case subjects ensures they are well matched on ascertainment-related factors that could otherwise introduce bias. Nonetheless, it will be important to confirm these results using a formal control group for comparison purposes. Third, although most individual HRV parameters were significantly different on a group level, there is clear overlap between patients with iRBD and control individuals, and sensitivities and specificities of single parameters provide only modest predictive value. There are several possible explanations. HRV as measured by EKG may be a relatively imprecise measure of CAD. However, the multivariable categorization model developed using discriminant analysis provided superior case classification accuracy; as a next step, this exploratory *post hoc* model needs to be tested in independent and nonselected populations to establish its predictive value. Alternatively, model precision likely reflects the heterogeneous nature of the iRBD group. Only some patients in our iRBD population are expected to develop a progressive synucleinopathy such as PD or DLB, and we do not yet know which of these patients will develop PD; so, definitive answer to this question will have to await long-term follow-up. In this regard, we hope to obtain additional information by recontacting these patients to determine whether or not they have developed evidence of neurodegenerative disease since their iRBD diagnosis. This prospective information will allow us to refine our predictive model.

Although the long-term goal of this research is to develop a screening tool for premotor PD, the most appropriate use of this tool can only be established based on future work. Subjects meeting certain preset criteria for HRV may require second-tier evaluation, perhaps with imaging studies as the final arbiter. Alternatively, it could prove that a multivariable HRV model, when combined with additional premotor features (e.g., hyposmia), will be an adequate predictor of underlying synucleinopathy. Regardless of the final constellation of tests eventually used, the successful development of disease modifying therapies likely rests on our ability to identify LBDs in their earliest stages, well before motor (and cognitive) features become apparent, when much less damage has occurred, and clinical trials aimed at disease modification are more likely to be successful.

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Author Roles: R Azhu Valappil was involved in organization and execution of the research project; review and critique of the statistical analysis; writing of the first draft, review and critique of the manuscript. JE Black was involved in conception and organization of the research project; critique of the manuscript. MJ Broderick was involved in organization of the research project; critique of the manuscript. O Carrillo was involved in organization of the research project, data retrieval; critique of the manuscript. E Frenette was involved in organization of the research project, record review, rescoring of the PSGs; critique of the manuscript, SS Sullivan was involved in organization of the research project, record review; critique of the manuscript. SM Goldman was involved in design, execution, review and critique of the statistical analysis; writing of the first draft, review and critique of the manuscript. CM Tanner was involved in conception of the research project; design, execution, review and critique of the statistical analysis; writing of the first draft, review and critique of the manuscript., James W Langston was involved in conception, organization and execution of the research project; review and critique of the statistical analysis; writing of the first draft, review and critique of the manuscript.

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