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RESEARCH ARTICLE

Short-term deceleration capacity of heart rate: a sensitive marker of cardiac autonomic dysfunction in idiopathic Parkinson's disease

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Abstract

Purpose Cardiac autonomic dysfunction in idiopathic Parkinson's disease (PD) manifests as reduced heart rate variability (HRV). In the present study, we explored the deceleration capacity of heart rate (DC) in patients with idiopathic PD, an advanced HRV marker that has proven clinical utility.

Methods Standard and advanced HRV measures derived from 7-min electrocardiograms in 20 idiopathic PD patients and 27 healthy controls were analyzed. HRV measures were compared using regression analysis, controlling for age, sex, and mean heart rate.

Results Significantly reduced HRV was found only in the subcohort of PD patients older than 60 years. Low- frequency power and global HRV measures were lower in patients than in controls, but standard beat-to-beat HRV markers (i.e., rMSSD and high-frequency power) were not significantly different between groups. DC was significantly reduced in the subcohort of PD patients older than 60 years compared to controls.

Conclusions Deceleration-related oscillations of HRV were significantly reduced in the older PD patients compared to healthy controls, suggesting that short-term DC may be a sensitive marker of cardiac autonomic dysfunction in PD. DC may be complementary to traditional markers of short-term HRV for the evaluation of autonomic modulation in PD. Further study to examine the association between DC and cardiac adverse events in PD is needed to clarify the clinical relevance of DC in this population.

Keywords Heart rate variability · Deceleration capacity of heart rate · Cardiac autonomic modulation · Idiopathic Parkinson's disease

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Introduction

Parkinson's disease (PD) is a neurodegenerative disease involving both the central and peripheral nervous systems, with significant heterogeneity of motor and non-motor symptoms [1]. Cardiac autonomic dysfunction is a common non-motor feature of PD and has been demonstrated by several methods that assess the variation in the time intervals between normal heartbeats. The application of these methods has consistently confirmed a reduced heart rate variability (HRV) in PD [2–4]. Significant reductions of the low-frequency (LF) spectral component of HRV have been extensively documented in patients with PD, and have been interpreted as reflecting arterial baroreflex dysfunction [2, 3, 5, 6]. Yet, results concerning cardiac parasympathetic modulation, as assessed by standard beat-to-beat measures derived from either short- or long-term HRV analysis, have not been consistent across studies. While some authors reported parasympathetic vagal dysfunction in both early and later stages of PD [3, 7–11], others have found no impairment of cardiac vagal modulation [5, 12–14].

An important observation to emerge from previous studies is that not all patients with PD manifest a reduction of cardiac parasympathetic modulation. For instance, prior work by some of the current authors found that in contrast to idiopathic PD, HRV is not reduced in PD patients who carry the G2019S mutation in the *LRRK2* gene [15]. In fact, we have recently confirmed that LRRK2-associated PD patients exhibit increased HRV markers of cardiac vagal modulation compared to healthy controls and to patients with idiopathic (sporadic) PD [16]. Thus, earlier HRV studies, by failing to discriminate between patients with familial and sporadic PD, may not have recognized the heterogeneity of cardiac parasympathetic regulation in this population. Besides genetic determinants of HRV, potential confounders including impaired cognition, olfaction, mood, behavior during rapid eye movement (REM) sleep, and motor functions may be associated with the integrity of cholinergic pathways in PD [17].

Deceleration capacity of heart rate (DC) is a measure of all deceleration-related oscillations of time intervals between heartbeats, which have been suggested to be more closely related to vagal chronotropic modulation [18–20]. Thus, DC captures all periodic modulations of HRV related to decelerations, that may become masked by the non-stationary nature of heart rate dynamics [21]. This non-linear HRV marker has proven clinical utility, and its predictive power for mortality after myocardial infarction has been found to be superior to standard measures for the analysis of short-term (< 30 min) HRV at rest [20]. Thus, the aim of the current study was to apply DC derived from short-term resting HRV analysis in order to evaluate cardiac autonomic modulation in idiopathic PD patients as compared to healthy individuals. We hypothesized that DC is a sensitive marker of cardiac autonomic dysfunction in idiopathic PD and, therefore, will manifest a significant effect of PD on the deceleration-related components of HRV assessed from short-term recordings. Autonomic symptoms are common but often unrecognized in patients with PD; thus, sensitive biomarkers that allow prompt recognition of autonomic dysfunction might result in earlier therapeutic intervention and increased quality of life in patients with PD.

Methods

Participants

We recruited 20 idiopathic PD patients and 27 healthy controls at the Toronto Western Hospital (Ontario, Canada) and the Parkinson's Institute (California, USA). Subjects with idiopathic PD were defined as individuals with PD, according to clinical diagnosis by a movement disorder specialist, in the absence of a family history of the disease in first- or second-degree relatives. All patients met UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [22]. Individuals taking anti-cholinergic medication, sympathetic agonists, or sympathetic antagonists or with evidence of thyroid dysregulation or diabetes were excluded from the study.

HRV analysis

Following 5 min of inactivity in a supine position, 7-min resting four-lead electrocardiograms (EKGs) (aV_R, aV_L, N, aV_F) were collected, under spontaneous breathing conditions, during daylight hours in a non-fasting state, and were digitized at 500 Hz using a laptop-based cardio-card EKG system (Nasiff Associates, Inc., NY, USA). Normal-to-normal (NN) cardiac interbeat intervals were extracted from the EKG recordings using Physionet WAVE v6.11 (www.physionet.org) in a Unix environment. The EKGs were manually checked for ectopic beats and regions of noise, which were manually removed, following the application of an automated algorithm for obtaining NN interval data [23]. Sequences of 300 consecutive NN intervals were automatically selected starting from the 81st sample of the recording.

Time domain HRV analysis included the calculation of the mean resting heart rate (HR), the standard deviation of the NN intervals (SDNN), the width of NN interval distribution (W), the coefficient of variation of the NN intervals (CV), and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD). For the

frequency domain HRV analysis, NN interval sequences of 215 s were transformed to evenly sampled time series with a 4.8 Hz resampling rate using the piecewise cubic Hermite function. HRV spectra were calculated using the fast Fourier transform (FFT) algorithm along with Welch's periodogram method (50% overlap window and a 256-sample window width). The power spectral density was calculated for the low-frequency (LF) band (0.04–0.15 Hz), the high-frequency (HF) band (0.15–0.4 Hz), and the total power (TP). The LF/HF ratio was also determined. DC was calculated using the *phase-rectified signal averaging algorithm*, based on averaging data segments around NN intervals longer than the preceding interval to quantify the average deceleration of heart rate [18]. *Information domain* analysis included the computation of multi-scale entropy measures to assess the irregularity of heart rate dynamics. Permutation entropy (PE), based on the probability of ordinal patterns of different length (λ) occurring over different timescales (τ) of the NN sequence, and Rényi entropy (RE) with different order α, based on the probability of NN sequences of length λ (4, 8, and 16), were calculated. (See Electronic Supplementary Material for further details on HRV methods).

The HRV measures included in the study account for markers of global (SDNN, W, CV, and TP), intermediate-term (LF power), and beat-to-beat (rMSSD and HF power) HRV. The advanced approaches (DC, PE, and RE) have provided better results compared to conventional measures in quantifying the variability or complexity of heart rate dynamics for the assessment of cardiac autonomic dysfunction in different clinical settings [20, 24–26].

Statistical analysis

Statistical analysis was performed using STATISTICA software (StatSoft, Inc., Tulsa, OK, USA). Continuous variables were assessed for normality by a Kolmogorov–Smirnov test and were natural log-transformed (Ln) to adjust for skewness when required. Group differences in HRV measures were assessed using multiple linear regression analysis adjusted for age, sex, and HR, whereas a *t*-test was applied for contrasting the remaining continuous variables. Group differences in sex distribution were assessed using the chi-square test. Correlations were assessed by the Pearson *r* coefficient. DC values were standardized (Z-scores) considering the mean value adjusted for age, sex, and HR through multiple regression analysis. The normal range for DC was considered to be the range within two standard deviations (SD) of the standardized mean of DC in the control group. Statistical significance was set at a p-value < 0.05, and adjusted for multiple comparisons in the case of multi-scale HRV analysis using the Benjamini–Hochberg correction to control for the false discovery rate at a q-value < 0.1.

Results

Demographic, clinical, and HRV characteristics of participants are shown in Table 1. All HRV measures were natural log-transformed. In both the PD and the control groups, age was significantly correlated with LF power ($r = -0.4$) and the measures of total HRV, i.e., SDNN, CV, and TP ($r = -0.5$). However, in the control group, but not in the PD group, age was significantly associated with the traditional beat-to-beat HRV markers, i.e., rMSSD ($r = -0.4$) and HF power ($r = -0.6$), as well as with DC ($r = -0.6$). No significant association was found between HRV and disease duration or age at onset. On preliminary multiple regression analysis including only the effect of PD as an independent predictor, LF power was found to be significantly reduced in the PD patients compared with controls ($t = -2.18$, $p = 0.03$). However, after adjustment for age, sex, and resting HR, most HRV measures were found to be significantly affected mainly by interindividual variations in age and HR. Age and resting HR were found to explain 44–61% of the total variance observed in the global HRV estimates, 55% of changes in LF power, and 34% of rMSSD variations. The sex of participants was also found to contribute significantly to the interindividual differences in HF power, DC, and LF/HF. Age, sex, and HR collectively explained 37% and 52% of differences in HF power and DC, respectively. A significant effect of PD was only seen in participants over 60 years of age (Table 2), for whom age was found to affect only LF and TP values. In this subcohort of patients, traditional analysis revealed a significant reduction of LF power, LF/HF, and global HRV measures, but the beat-to-beat HRV markers rMSSD and HF power were not significantly reduced. The non-linear HRV measure DC, however, was significantly lower in the subcohort of PD patients over 60 years of age than in the healthy controls. Moreover, 15% of patients in the whole PD group ($n = 3$) and 17% of patients in the subcohort of individuals over 60 years old ($n = 2$), showed a DC Z-score below the normal range of the control group (i.e., lower than mean $DC_{Control}$ Z-score − 2SD). Among these patients, two cases from the whole PD group showed DC ≤ 2.5 ms. The regression analysis was repeated after excluding 11 PD patients who showed a more irregular cardiac rhythm that could affect the analysis of HRV, but the same significant findings between the PD and control groups were obtained. No significant between groups differences were found for PE and RE.

Discussion

In the present study, we quantified the deceleration-related modulations of HRV, assessed from short-term ECG recordings at rest in patients with idiopathic PD. Our main result is that DC was found to be sensitive to differences in rapid

Table 1 Demographic, clinical, and heart rate variability characteristics of participants

Feature	PD ($n=20$)	Control ($n=27$)	t value	p value
Female/Male	10/10	15/12	*	0.706
Age (years)	64.2 ± 10.8 (45–82)	58.7 ± 13.9 (20–77)	− 1.45	0.153
Disease duration (years)	6.3 ± 6.0 (0–20)	–		–
SCOPA-AUT	12.8 ± 6.2 (2.0–20.0)	8.5 ± 6.7 (2.0–24.0)	− 1.73	0.095
HR (bpm)	69 ± 7 (58–79)	69 ± 11 (51–108)	–	–
Ln HR	4.23 ± 0.10 (4.06–4.43)	4.22 ± 0.15 (3.93–4.68)	− 0.37	0.713
Global HRV				
Ln SDNN	3.19 ± 0.51 (2.30–4.23)	3.45 ± 0.46 (2.08–4.42)	− 1.13	0.264
Ln W	4.98 ± 0.51 (3.95–6.12)	5.21 ± 0.45 (3.78–6.05)	− 0.92	0.364
Ln CV	1.03 ± 0.45 (0.18–1.90)	1.27 ± 0.42 (0.34–2.27)	− 1.05	0.298
Ln TP	2.39 ± 0.10 (2.21–2.58)	2.44 ± 0.09 (2.19–2.61)	− 1.03	0.311
Intermediate-term HRV				
Ln LF	2.32 ± 0.12 (2.12–2.55)	2.38 ± 0.10 (2.10–2.56)	− 1.54	0.131
Beat-to-beat HRV				
Ln rMSSD	2.80 ± 0.56 (1.75–3.75)	2.92 ± 0.55 (1.42–4.04)	0.21	0.832
Ln HF	2.25 ± 0.12 (2.00–2.47)	2.29 ± 0.12 (2.02–2.52)	− 0.18	0.855
Ln DC	1.68 ± 0.64 (0.64–2.87)	1.98 ± 0.59 (0.74–3.23)	− 0.79	0.436
Ln LF/HF	0.068 ± 0.10 (−0.10 to 0.22)	0.10 ± 0.08 (− 0.05 to 0.24)	− 1.16	0.255

Values are expressed as mean ± standard deviation (range) or number of cases (n). Between groups differences in sex distribution were analyzed using a chi-square test; age, disease duration, and SCOPA-AUT score using a t-test, and mean heart rate using a multiple regression analysis adjusted for age, sex, and the effect of age and sex interaction. Differences in heart rate variability measures were assessed through multiple regression analysis adjusted for age, sex, and mean heart rate. *$\chi^2=0.14$. *SCOPA-AUT* Scales for Outcomes in Parkinson's disease–autonomic symptoms score; *HR* mean heart rate; *Ln* natural log-transformed; *SDNN* standard deviation; *W* width, difference between the longest and shortest normal-to-normal intervals; *CV* coefficient of variation; *TP* power spectral density of the total power band (0.04–0.4 Hz); *LF* power spectral density of the low-frequency band (0.04–0.15 Hz); *rMSSD* square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals; *HF* power spectral density of the high-frequency band (0.15–0.4 Hz); *DC* deceleration capacity of heart rate

oscillations of cardiac rhythm in the subcohort of patients with PD over the age of 60.

In keeping with previous reports, advancing age, increasing HR, and male sex were significantly associated with lower values of HF power, whereas only advancing age and increasing HR were found to be significant determinants of lower rMSSD values [27–29]. These findings suggest that inconsistent reports in relation to cardiac vagal modulation in PD may arise from the effects of potential confounding factors [2, 8, 13, 30]. For instance, lower rMSSD values have been reported in PD patients who were older, exhibited greater HR or had shorter heart period than the healthy control participants [30–32]. The LF component of HRV was significantly reduced in the PD group before controlling for the effect of possible confounders. However, the decline in LF power was significantly associated with advancing age and increasing resting HR, which collectively explained 55% of its variance. Our results are consistent with prior work where age and HR were found to be the major determinants of LF and HF power [28], and further highlight the need to control for their confounding effects. Matching patient and control groups for age and sex may be appropriate to control for the effect of these demographic factors, but further strategies may be necessary to adjust for the effect of HR [33].

Consistent with previous reports, we found that PD patients over 60 years of age had lower values of LF power, LF/HF, and global HRV measures than healthy controls, suggesting impairment of arterial baroreflex and overall cardiac autonomic functioning [2, 3, 12]. Aging is the main modifying factor on the phenotypic presentation, course, and progression of PD [34]. Taken together, our results suggest that impaired cardiac autonomic modulation in older PD patients is associated with the accumulation of age-related somatic damage combined with progressive failure of compensatory mechanisms in the autonomic nervous system. In keeping with this possibility, age was recently found to be a crucial factor in animal models for the aggregation and complete propagation to the heart of alpha-synuclein, a key protein involved in PD pathology [35].

The beat-to-beat HRV measures, rMSSD and HF power, were not significantly reduced in the older PD patients. Consistent with this, previous work in 20 de novo and 19

Table 2 Demographic, clinical, and heart rate variability characteristics of participants over 60 years of age

Feature	PD ($n=12$)	Control ($n=15$)	t value	p value
Female/Male	8/4	7/8	*	0.516
Age (years)	70.8 ± 7.7 (62–82)	68.8 ± 5.7 (62–77)	0.76	0.455
Disease duration (years)	8.4 ± 6.8 (1–20)	–	–	–
HR (bpm)	70 ± 5 (60–79)	66 ± 9 (51–81)	–	–
Ln HR	4.24 ± 0.08 (4.09–4.37)	4.17 ± 0.14 (3.93–4.39)	1.66	0.109
Global HRV				
Ln SDNN	2.99 ± 0.38 (2.30–3.47)	3.39 ± 0.27 (2.94–3.87)	**− 3.16**	**0.004**
Ln W	4.79 ± 0.41 (3.95–5.53)	5.17 ± 0.22 (4.82–5.55)	**− 3.15**	**0.004**
Ln CV	0.84 ± 0.36 (0.18–1.28)	1.17 ± 0.31 (0.79–1.81)	**− 2.52**	**0.019**
Ln TP	2.35 ± 0.08 (2.21–2.46)	2.42 ± 0.06 (2.33–2.53)	**− 2.61**	**0.015**
Intermediate-term HRV				
Ln LF	2.27 ± 0.09 (2.12–2.38)	2.37 ± 0.07 (2.25–2.49)	**− 3.43**	**0.002**
Beat-to-beat HRV				
Ln rMSSD	2.68 ± 0.51 (1.75–3.43)	2.81 ± 0.36 (2.39–2.50)	−0.75	0.463
Ln HF	2.22 ± 0.12 (2.00–2.41)	2.25 ± 0.08 (2.08–2.44)	−0.76	0.455
Ln DC	1.46 ± 0.47 (0.64–2.23)	1.79 ± 0.35 (1.34–2.55)	**− 2.13**	**0.043**
Ln LF/HF	0.05 ± 0.10 (-0.09–0.16)	0.12 ± 0.08 (− 0.01–0.24)	**− 2.19**	**0.038**

Values are expressed as mean ± standard deviation (range) or number of cases (n). Between groups differences in sex distribution were analyzed using a Chi-Square test, and age, mean heart rate and disease duration using a t-test. Differences in Ln LF and Ln TP were assessed through multiple regression analysis adjusted for age. No adjustment was made for the remaining heart rate variability measures. Significant p-values appear in bold style. *Yates corrected $\chi^2 = 0.42$. HR: mean heart rate; Ln: natural log-transformed; SDNN: standard deviation; W: width, difference between the longest and shortest normal-to-normal intervals; CV: coefficient of variation; TP: power spectral density of the total power band (0.04–0.4 Hz); LF: power spectral density of the low frequency band (0.04–0.15 Hz); rMSSD: square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals; HF: power spectral density of the high frequency band (0.15–0.4 Hz); DC: deceleration capacity of heart rate

treated PD patients without orthostatic hypotension (OH) reported intact vagal regulation, as assessed by standard short-term HRV analysis at rest [5, 12]. OH is a key manifestation of cardiovascular dysautonomia in PD that involves both the parasympathetic and sympathetic components of the arterial baroreflex [36]. Yet, cardiac parasympathetic dysfunction has been found in 14 de novo patients without OH using standardized cardiovascular autonomic tests [37], 32 untreated patients using traditional short-term HRV analysis [8], and seven early patients with no clinical signs of autonomic dysfunction, using traditional HRV analysis from 24-h ambulatory recording [10]. An important concern, however, is that no significant differences in rMSSD or HF power were found in a group of 48 PD patients compared to 30 healthy controls, despite the patients showing a significantly reduced beat-to-beat HRV as assessed by pNN50 (the percentage of NN intervals differing more than 50 ms from each other) from 24-h recordings [38]. Findings from previous studies further suggest the occurrence of feature clustering within the wide clinical variability of PD [39, 40]. Consistently, several manifestations such as motor clinical phenotype [2], olfactory dysfunction [11], REM sleep behavior disorder [41], and mild cognitive impairment [42] have been also associated with cardiac cholinergic dysfunction.

DC was significantly reduced in the older group of PD patients, consistent with previous work reporting a reduction of DC assessed from long-term ECG recordings in 10 PD patients compared to 60 healthy controls [43]. Reduced DC in the PD patients suggest impaired cardiac autonomic modulation, which could be related to parasympathetic dysfunction [18–20, 44]. In previous work we found that, in contrast to the global measures of HRV, DC was not sensitive to cardiac sympathetic activation by orthostatic challenge [46]. In the present study, reduced DC was observed in the PD patients despite no significant differences in the markers of beat-to-beat variability and complexity of HR dynamics. Taken together, these findings suggest that DC provides additional information on HRV to that obtained with the traditional and complexity measures. In keeping with our findings, DC has been found to be more sensitive than traditional HRV measurements as a marker for cardiac autonomic changes with aging [44]. However, the weak association of age with DC among the PD patients, in contrast to its strong correlation in the control group, suggest that factors other than age may also contribute to a reduction of deceleration-related oscillations of HR in patients with PD.

Reduced short-term (2–15 min) HRV has been associated with sudden death [47], and patients with low parasympathetic activity have been reported to have a risk for sudden death approximately double than that of those with high parasympathetic activity [48]. Mortality in PD is higher compared to the general population, and one in six patients with PD (17%) may die suddenly [49]. The causes of sudden unexpected death in PD (SUDPAR) are unknown, but cardiac autonomic dysfunction may play an important role [50, 51]. In our study, 17% of PD patients over 60 years of age showed DC values below the normal range observed in the control group. Values of short-term resting DC ≤ 2.5 ms have been previously shown to be a very powerful predictor of mortality after myocardial infarction [20]. Further studies are needed to explore whether reduced DC in patients with PD is associated with a greater risk of SUDPAR.

We acknowledge some limitations. Our study was conducted in a small sample size. A large effect size has been observed, however, for traditional markers of beat-to-beat HRV in PD, and consistent with this, significant differences have been detected with appropriate statistical power in data sets with a small sample size [3, 8]. These findings further emphasize that traditional beat-to-beat HRV measures yield inconsistent results in PD and should therefore be interpreted with caution. ECG recordings were obtained under spontaneous breathing conditions. However, a significant effect of respiratory rate has not been observed for all HRV measures [52]. Furthermore, the effect of breathing has been shown to decrease by controlling for baseline HR and by participants avoiding irregular respiration [53, 54]. Since several clinical correlates of cholinergic dysfunction have been identified [17, 55], their assessment should also be considered when evaluating cardiac parasympathetic regulation in PD. The study patients were receiving L-dopa treatment which might have influenced autonomic control, although no significant effect of dopaminergic therapy on cardiac autonomic function was previously reported in PD patients [4, 56]. Quantitative evaluation using standardized cardiovascular reflex tests would have been useful to confirm autonomic dysfunction in the PD patients [45]. In keeping with previous work, we found no differences in HR irregularity between the PD and control groups [8], although longer recording lengths may be more appropriate for entropy analysis [57]. Other complexity methods have proven useful for the analysis of HRV in PD [58–60].

Conclusions

Deceleration-related oscillations of HRV were significantly reduced in the older PD patients, suggesting that DC derived from short-term HRV analysis at rest may be a sensitive marker of cardiac autonomic dysfunction in idiopathic PD. The effect of age on DC and its ability to identify adverse changes in cardiac autonomic modulation needs to be considered and explored in this context. DC may be complementary to traditional markers of short-term HRV analysis for the evaluation of autonomic modulation in PD. Autonomic dysfunction is prevalent in PD and the most prominent cardiac abnormality in these patients is cardiac autonomic dysfunction. Further study to examine the association between DC and cardiac adverse events in PD is needed to clarify the clinical relevance of DC in this population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10286-021-00815-4.

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Declarations

Conflict of interest CM has received research grants from the Michael J. Fox Foundation, Canadian Institutes of Health Research, Parkinson's Foundation (US), National Institutes of Health (US), and International Parkinson and Movement Disorders Society. She is a consultant for Grey Matter Technologies and receives financial compensation as a steering committee member from the Michael J. Fox Foundation. The remaining authors declare that they have no conflict of interest.

Ethical standards The study protocol was approved by the University Health Network Research Ethics Board (Toronto) and El Camino Hospital Institutional Review Board (Parkinson's Institute). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All participants provided written informed consent prior to their inclusion in the study.

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Short-term deceleration capacity of heart rate: a sensitive marker of cardiac autonomic dysfunction in idiopathic Parkinson's disease

Clinical Autonomic Research

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Electronic Supplementary Material

SUPPLEMENTARY METHODS

Heart rate variability analysis

Time domain statistical measures of HRV primary analysis, as well as DC and AC, were calculated with the VFC32 software (Machado & Estévez, 2008). For *frequency domain* HRV analysis, digital signal processing was carried out using software developed with MATLAB R2013b (The MathWorks, Inc., Natick, Massachusetts) (as suggested by previous work) (Estévez et al., 2016; Wen & He, 2011). Ordinal NN sequences were resampled by using the piecewise cubic Hermite function. Since the time length of the NN series was 215 seconds and 1024 samples were taken for spectral analysis, the resulting sampling period was 210 ms. The preprocessing procedures included: (a) NN series demeaning, by subtracting the mean NN value from all the items in the series; (b) standard linear detrending to avoid possible drifts in the series; (c) high-pass digital filtering (cut-off frequency of 0.02 Hz) using a sixth order Butterworth infinite impulse response filter; (d) zero-phase-shift digital filtering of the NN series. The power spectral density (PSD) was estimated by applying the Welch periodogram method (Welch, 1967) and the fast Fourier transform (FFT) algorithm. Each sliding window of 1024 samples was submitted to the computation of the Welch modified periodogram with a Hamming window, using segments of 256 samples and overlapping periods of 128 samples. The FFT was applied to each of these segments. The frequency resolution of the spectral process was 0.005 Hz.
From *information domain* methods, Rényi entropy H_R algorithm was developed over C++ (Equation 1), and permutation entropy H_p codes were implemented in MATLAB (Equation 4).

$$H_R(\alpha,\sigma,\lambda) = \frac{1}{1-\alpha} log_2 \left(\sum_{i=1}^{n_{seq}} p_{seq_i}^{\alpha} \right) \quad (1)$$

where p_{seq_i} is the probability of a sequence of NN intervals of length $\lambda = \{4, 8, 16\}$, the exponent $\alpha = \{-5, -4, -3, -2, -1, +1, +2, +3, +4, +5\}$ is the order of the entropy measure, and n_{seq} is the total number of NN sequences in the original sequence. The probability of a sequence of NN intervals was estimated by measuring the similarity of the sample i with all other samples of the same length λ in the whole sequence. Each sequence was regarded as a point in a λ-dimensional space, and its probability was estimated using a Gaussian kernel centered on each such point (Cornforth et al., 2014). Then p_{seq_i} is given by the density function:

$$p_{seq_i} = \sum_{j=0}^{n} exp\left(\frac{-dist_{ij}^2}{2\sigma^2} \right) \quad (2)$$

where σ is the Gaussian dispersion or tolerance and $dist_{ij}$ is the Euclidean distance between sample i and all other samples j, in λ-dimensions:

$$dist_{ij} = \sum_{k=0}^{\lambda} \left(x_{i+k} - x_{j+k}\right)^2 \quad (3)$$

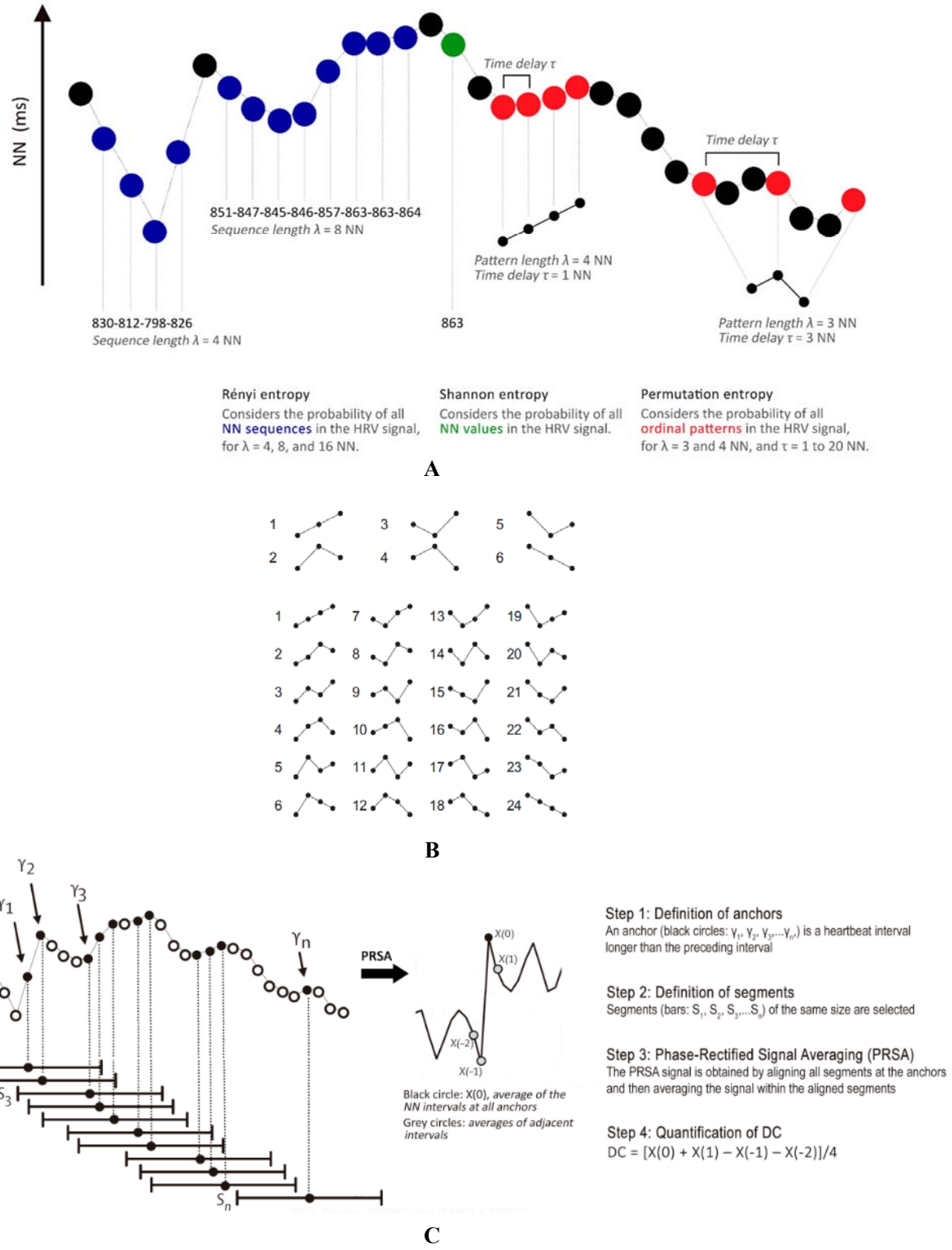
Here, x_{i+k} is one NN sample out of sequence of length λ, the pattern length over which comparison occurs. In order to estimate the probabilities of NN sequences, different sets of values of tolerances $\sigma = \{0.2, 0.3, 0.5\}$, $\sigma = \{0.5, 0.8, 1.3\}$, $\sigma = \{1.0, 1.6, 2.5\}$, were considered for each length λ, respectively.

PE is defined as the normalized Shannon entropy associated with the frequency distribution of the ordinal patterns π occurring within a time series (Bandt & Pompe, 2002):

$$H_p(\lambda, \tau) = -\frac{1}{log_2 \lambda!} \sum_{i=1}^{\lambda!} P_\pi(\lambda, \tau, i) log_2[P_\pi(\lambda, \tau, i)] \quad (4)$$

Here, i is the permutation index that identifies the ordinal pattern or motif of length $\lambda = \{3,4\}$ over the temporal scale (time delay) $\tau = \{1..20\}$. $P_\pi(\lambda, \tau, i)$ is the probability of the ordinal pattern π. Motifs and their corresponding permutation indexes appear in WEM Figure 1.

SUPPLEMENTARY FIGURE



Supplementary Figure 1. Novel features of heart rate variability analysis. a, Information domain measures. b, Ordinal patterns of length λ = 3 and λ = 4 and their corresponding permutation indexes. For each pattern, the amplitudes (vertical axis) of the values are plotted *vs.* time (horizontal axis). c, Phase-Rectified Signal Averaging (PRSA) and quantification of deceleration capacity of heart rate (DC). NN: normal-to-normal cardiac interbeat intervals. The figure was reproduced and modified from the publications of Parlitz *et al.* (2012) and Bauer *et al.* (2006)

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