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Joint Symbolic Dynamics as a Model-Free Approach to Study Interdependence in Cardio-Respiratory Time Series

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***Abstract*— Heart rate and respiration display fluctuations that are interlinked by central regulatory mechanisms of the autonomic nervous system (ANS). Joint assessment of respiratory time series along with heart rate variability (HRV) may therefore provide information on ANS dysfunction. The aim of this study was to investigate cardio-respiratory interaction in patients with Parkinson's disease (PD), a neurodegenerative disorder that is associated with progressive ANS dysfunction. Short-term ECG and respiration were recorded in 25 PD patients and 28 healthy controls during rest. To assess ANS dysfunction we analyzed joint symbolic dynamics of heart rate and respiration, cardio-respiratory synchrograms along with heart rate variability. Neither HRV nor cardio-respiratory synchrograms were significantly altered in PD patients. Symbolic analysis, however, identified a significant reduction in cardio-respiratory interactions in PD patients compared to healthy controls (16 ± 3.6 % vs. 20 ± 6.1 %; p = 0.02). In conclusion, joint symbolic analysis of cardio-respiratory dynamics provides a powerful tool to detect early signs of autonomic nervous system dysfunction in Parkinson's disease patients at an early stage of the disease.**

I. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is associated with progressive autonomic nervous system dysfunction. The brainstem is affected from an early stage of the disease resulting in ANS dysfunction [1]. Radio-labeled MIBG scintigraphy identified cardiac sympathetic dysinnervation preceding clinical symptoms of somatomotor dysfunction in some patients with PD [2]. Analyses of heart rate variability (HRV) have provided further evidence for ANS dysfunction in PD [3]. It has been suggested that ANS dysfunction may provide a biomarker for early detection of PD although this may seem overly simplistic [4].

Heart rate variability analysis provides a simple tool to study changes in neural outflow to the heart, using noninvasive body surface ECG. As HRV is heavily influenced by respiration, in particular during rest, its interpretation remains difficult without concurrent assessment of breathing. Cardio-respiratory interdependence has been previously studied by exploiting coherence in their power spectra [5] or mutual information among others [6]. One of the most commonly used approaches is the synchrogram technique [7]. We have recently proposed a novel technique to study cardio-respiratory coordination based on joint symbolic dynamics [8]. Symbolic dynamics was originally introduced to cardiovascular time series analysis for quantifying nonlinear HRV [9] followed by joint analysis of heart rate and blood pressure interactions [10, 11].

The aim of this study was to investigate whether assessment of cardio-respiratory interdependence using joint symbolic dynamics may provide additional information to heart rate variability analysis, and hence a sensitive tool for detecting early signs of ANS dysfunction in patients with Parkinson's disease.

II. Methods

A. Joint symbolic dynamics of cardio-respiratory signals

To obtain a symbolic representation of cardio-respiratory dynamics we first considered the R peak locations from the body surface ECG, using an automated algorithm. From the series of R peaks we computed beat-to-beat intervals (RR) of cardiac cycles. Next we obtained the instantaneous phase of the respiratory signal at the time of each R peak in the ECG, using the Hilbert transform, yielding beat-to-beat values of respiratory phase (RP). From these two time series of RR and RP we derived two symbolic sequences, *sHR* (HR denoting heart rate, i.e. the reciprocal of RR interval) and *sRP* based on the differences between successive beats, using the transformation rule below, as described previously [8]:

$$sHR_i = \begin{cases} 0 \text{ if } \mathrm{RR}_{i+1} - \mathrm{RR}_i > 0 \\ 1 \text{ if } \mathrm{RR}_{i+1} - \mathrm{RR}_i < 0 \\ 2 \text{ if } \mathrm{RR}_{i+1} - \mathrm{RR}_i = 0 \end{cases} \quad (1)$$

$$sRP_i = \begin{cases} 0 \text{ if } |\mathrm{RP}_{i+1}| - |\mathrm{RP}_i| > 0 \\ 1 \text{ if } |\mathrm{RP}_{i+1}| - |\mathrm{RP}_i| < 0 \\ 2 \text{ if } |\mathrm{RP}_{i+1}| - |\mathrm{RP}_i| = 0 \end{cases} \quad (2)$$

Based on the symbol sequences *sHR* and *sRP*, series of words of length two were derived (*wHR* and *wRP*) that contain two successive symbols of *sHR* and *sRP*, respectively. Thus, the dynamics in each time series (RR and RP) is represented by 3 x 3 = 9 different word types.

The interaction between cardiac and respiratory signals was then studied by comparing the temporal relationship

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between specific word types in the HR and RP domains. Given the encoding of dynamics via three different symbols forming words of length two, 3^2 x 3^2 = 81 combinations of word types may occur. To deal with relatively short recordings that would result in low statistical representation of particular word types we collated word types: if the word type in one domain was identical to that of the other domain (i.e. $wHR[i] = wRP[i]$), the cardiac and respiratory epochs were considered to be coordinated. The percentage of interaction was then quantified by dividing the total count of coordinated words by the total number of words.

B. Synchrogram analysis

The synchrogram technique has been developed to study the relationship between cardiac respiratory oscillators and is described in detail elsewhere [7]. Briefly, each R-R interval is considered a cardiac cycle (2π) and the phase of respiratory cycle at the occurrence of an R-peak is estimated using the Hilbert transform. Subsequently, transient epochs of m : n phase-locking ratios (i.e. heart beats : respiratory cycle) are estimated.

We calculated the percentage of recording that displayed phase-locking between heart rate and respiratory oscillators to obtain a quantitative measure of cardio-respiratory synchronization.

C. Heart rate variability analysis

For traditional time domain analysis of HRV [12], we computed *meanNN*–the mean beat-to-beat interval of normal heart beats; *sdNN*–standard deviation of NN intervals; and *RMSSD*–the root-mean-square of successive beat-to-beat differences.

For frequency domain analysis of HRV we generated equidistant time series, using a linear interpolation at 500 ms sampling intervals. The power spectrum was then estimated, using the Fast Fourier Transform according to HRV Task Force recommendations: *LF*–low frequency power (0.04-0.15 Hz) and *HF*–high frequency power (0.15-0.4 Hz).

Nonlinear characteristics of HRV were quantified according to the symbolic dynamics approach described by Porta *et al.* [13]. Here, the series of RR intervals was transformed into an alphabet of six symbols {0, 1, 2, 3, 4, 5}. As a transform rule, non-uniform quantization was applied, keeping the number of points associated with each quantization level constant [14].

The patterns of symbolic sequences of length three were grouped into four families according to the number and types of variations from one symbol to the next one. The pattern families were: 1) patterns with no variation (*0V*–all three symbols are equal); 2) patterns with one variation (*1V*–two consecutive symbols are equal and the remaining one is different); 3) patterns with two like variations (*2LV*–the three symbols form an ascending or descending ramp), 4) patterns with two unlike variations (*2UV*–the three symbols form a peak or a valley). The rates of occurrence of these patterns are indicated as *0V%*, *1V%, 2LV%* and *2UV%*.

D. Study subjects

In this study we investigated 25 patients with PD aged between 61 and 84 years and 28 healthy subjects aged between 59 and 91 years. Original HRV and blood pressure variability data have been reported previously as part of a bigger study [15]. Parkinson's disease participants fulfilled the Parkinson's disease Society Brain Bank clinical criteria [16] and were in the early stages of the disease, with mild to moderate impairment (Hoehn and Yahr scores < 2.5) [17] and were all medicated with L-dopa. The subjects in the reference group were free from any neurological disease and not on any medication that would affect the ANS.

The study was approved by the Human Research Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service. All participants provided written informed consent.

E. Data recording and signal pre-processing

High resolution body surface ECG (lead II) was recorded for ten minutes at a sampling rate of 2 kHz via standard Ag-AgCl electrodes using a Powerlab® system (ADInstruments, Australia). Respiration was recorded simultaneously via a strain gauge transducer attached to a strap around the chest (Pneumotrace®, Morro Bay, USA).

Subjects were studied in a supine position at a comfortable ambient temperature. Care was taken to ensure a calm and quiet environment to minimize spontaneous arousal responses. For further analysis, we considered the last five minutes of recording.

Custom written computer software developed in MATLAB® was used to detect R peaks in the ECG recording. A parabola was fitted around the R wave to determine the R wave maximum. The RR time series were visually scanned for artifacts. Ectopic beats were replaced with the average RR interval calculated from the beat prior to and after ectopy.

Respiratory signals were low-pass filtered at 1.0 Hz to remove noise, using a zero-phase forward and reverse digital filter, which first filtered the raw signal in the forward direction using a 4^{th} order Butterworth filter, and subsequently filtered the time reversed signal. The resultant signal has zero phase distortion. To detect inspiratory onsets for each respiratory cycle the offset of the signal was removed by subtracting the time average. Subsequently, the inspiratory and expiratory onsets were determined as the zero-crossings of the first derivative of the respiratory signal. All zero-crossings less than 1.0 second apart were considered as artifacts and hence discarded. The inspiratory onsets of respiration were later used to calculate the average respiratory time period.

F. Statistical analysis

For statistical analysis of cardio-respiratory variables and HRV measures we employed the two-sided t-test. A p-value < 0.05 was considered statistically significant. Data are presented as group means and standard deviations.

III. RESULTS

Nine recordings of the PD group and five recordings of the reference groups were discarded from analysis due to the presence of frequent ectopic beats or poor quality of the respiratory signal.

TABLE I. COMPARISON OF HEART RATE VARIABILITY BETWEEN PARKINSONS DISEASE (PD) PATIENTS AND HEALTHY CONTROLS (CON).

HRV measure	PD	CON	*p*-value
meanNN	900 ± 103	894 ± 154	0.8
sdNN	25 ± 11	26 ± 12	0.7
RMSSD	12 ± 9	13 ± 8	0.5
logLF	1.86 ± 0.49	1.94 ± 0.51	0.6
logHF	1.60 ± 0.46	1.70 ± 0.46	0.4
0V%	31 ± 15	31 ± 15	0.9
1V%	46 ± 8	44 ± 8	0.4
2LV%	6.9 ± 5.2	7.6 ± 7.0	0.7
2UV%	17 ± 12	18 ± 13	0.8

The mean RR interval (meanNN) was comparable between both groups (Tab. 1). The mean respiratory interval tended to be shorter in PD patients compared to controls (4.6 ± 0.6 s vs. 4.9 ± 0.6 s; $p = 0.11$). None of the linear and non-linear heart rate variability measures was significantly different between PD and reference subjects (Tab 1).

Joint symbolic analysis of cardio-respiratory dynamics revealed a significant reduction in the relative frequency of symmetric RR and RP patterns (i.e. $wHR[i] = wRP[i]$) in patients with PD compared to controls, indicating a loss of cardio-respiratory coordination (16 ± 3.6 % vs. 20 ± 6.1 %; $p = 0.02$, Fig. 1).

Synchrogram analysis showed a trend towards reduced cardio-respiratory synchronization in PD patients, but this trend did not reach statistical significance (21 ± 4.4 % vs. 25 ± 6.4 %; $p = 0.09$). Analysis of predominant phase locking ratios demonstrated 3:1 to be most common in controls (57 % of subjects) followed by 4:1 (30 % of subjects). In PD patients, 3:1 and 4:1 ratios were equally common (44 % of patients each).

Correlation analysis between synchrogram based and joint symbolic dynamics based estimates of cardio-respiratory synchronizations showed no significant linear association between both variables of cardio-respiratory coordination (Pearson's $r = 0.1$).

IV. DISCUSSION

The main finding of our study is a reduction in cardio-respiratory interaction in patients with Parkinson's disease at an early stage of the disease, despite normal heart rate variability.

Parkinson's disease has been associated with ANS and several studies reported significant changes in HRV [3]. Our own data, however, do not confirm these observations. Even though we investigated a wide range of HRV measures that capture both, linear and nonlinear aspects, we observed comparably normal HRV values in patients with PD. A reason for this discrepancy with other studies may be the relative small sample size and the fact that our patients were at an early stage of the disease. Further, the duration of recording that was considered for this study was relatively short (five minutes).

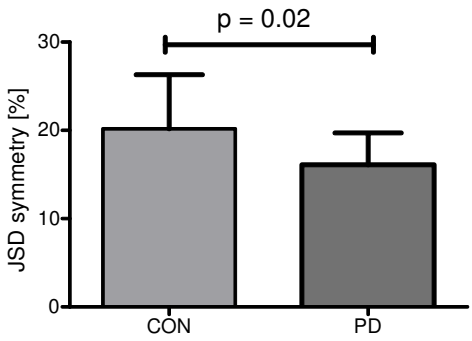

Figure 1. Percentage of symmetric word types in symbolic dynamics of RR intervals and respiratory phases in patients with Parkinson's disease (PD) and healthy controls (CON).

Although the respiratory rate tended to be slightly elevated in our PD patients, only the joint assessment of respiratory dynamics along with heart rate dynamics was able to reveal changes in ANS function, i.e. the interplay between breathing and heart beat of patients with PD. Since HRV was preserved in PD patients we assume that mainly differences in breathing patterns contributed to the reduction in cardio-respiratory coordination. It is not clear whether this reduction has any physiological implications.

Comparing the well established synchrogram technique with our recently developed symbolic approach, both techniques indicate changes in the cardio-respiratory control of PD patients, the later confirming our findings obtained from the analysis of JSD. The symbolic approach, however, appears to be more sensitive to these alterations, as demonstrated by lower *p*-values in the *t*-test results. Correlation analysis demonstrated that symbolic analysis of cardio-respiratory interaction provides information that is at least partly independent of that obtained with the synchrogram technique.

V. CONCLUSION

Joint symbolic analysis of ECG and respiration provides a powerful technique to assess cardio-respiratory dynamics. Our data suggest subtle autonomic nervous system dysfunction in patients at an early stage of Parkinson's disease. Importantly, these changes could not be demonstrated with standard analyses of heart rate variability.

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