Assessment of Joint Interactions between Respiration and Baroreflex Activity using Joint Symbolic Dynamics in Heart Failure Patients

Muammar M Kabir, Elyar Ghafoori, Larisa G Tereshchenko

Oregon Health and Science University, Knight Cardiovascular Institute, Portland, OR, USA

Abstract

In this paper we employed a novel approach based on joint symbolic dynamics (JSD) to study interaction between respiratory phase and baroreflex activity. Electrocardiogram (ECG) and blood pressure recordings from six participants with history of heart failure were included in this study. First, the ECG R-peaks and systolic blood pressure indices were detected using parabolic fitting. Second, the respiratory signal was derived from Frank orthogonal ECG leads using QRS slopes and R-wave angles. Third, time series of R-R intervals and systolic blood pressure (SBP) were extracted, and respiratory phases were obtained using the Hilbert transform. Subsequently, each series was transformed into binary symbol vectors based on their successive changes and words of length '2' were formed. Baroreflex patterns were studied using word combinations representing baroreflex activity for specific changes in respiratory phases. Baroreflex activity was significantly higher for alternating low-high/high-low heart rate and SBP during inspiration as compared to continuous increase or decrease in heart rate and SBP ($w_i^{SBP}=10, w_i^{HR}=01, w^{RP}=11$: 39.1±9.3% vs. $w_i^{SBP}=00, w_i^{HR}=11, w^{RP}=11$: 6.4±3.9%, $p<0.0001$).

1. Introduction

The study of inter-relationship between respiration and baroreflex responsiveness may provide early indicators of autonomic dysfunction [1]. However, the interplay between respiratory sinus arrhythmia and baroreflex activity is understood to result in complex behavior.

Compared to conventional signal-processing approaches which are inadequate for characterizing complex system dynamics, joint symbolic dynamics (JSD) provides an effective technique by employing a coarse-graining procedure to preserve the robust properties of the system's complex dynamics and providing easy interpretation of physiological data by offering a framework for exploring the nature of a system through a means of simplified analysis [2,3]. Symbolic dynamics has been suggested to provide improved performance for the analysis of respiratory data and cardiorespiratory interaction and an efficient technique for the quantification of respiration-baroreflex inter-relationship [3-5].

In patients suffering from dilated cardiomyopathy, the alternation between low to high blood pressure and heart rate has been demonstrated to be significantly higher compared to healthy controls [6]. However, combined analysis of respiration and baroreflex function has never been studied in heart failure patients. This study was conducted to quantify respiration-baroreflex inter-relationship using JSD approach in heart failure patients.

2. Methods

The study conformed to principles outlined in the Declaration of Helsinki and was approved by the local ethics committee. Each participant provided written informed consent.

2.1. Subjects

This study population was composed of 6 participants of the ongoing prospective cohort study "Reverse Electrical Remodeling of Native Conduction", which enrolled adult heart failure patients with approved indications per ACC/AHA/HRS guidelines for implantation of a cardiac resynchronization therapy defibrillator (CRT-D), who were in sinus rhythm at the time of enrollment. Mean age was 67.8±11.8 years, more than half were female (N=4; 67%) and white (N=5; 83%). Almost all patients (N=5; 83%) have had ischemic cardiomyopathy with mean left ventricular ejection fraction 24.2±9.2 %. More than half of study participants have had NYHA class I-II (N=4; 67%), and 33% have had class III. Mean QRS duration was 158.5±15.2 ms. Most of patients (N=5; 83%) have had left bundle branch block.

2.2. Data recording

High resolution (1000Hz) 12-lead ECG was recorded continuously at rest for at least 30 minutes via H12+™

digital Holter recorder (Mortara Instruments, Milwaukee, WI), simultaneously with digital blood pressure waveform. Output of CNAP 500 continuous noninvasive hemodynamics monitor (CNSystems Medizintechnik AG, Austria) was digitized using the NI USB-9215A portable data acquisition system, with customized LabVIEW (National Instruments, Austin, TX) software application. Recording was performed before CRT-D implantation.

2.3. ECG and SBP processing

Custom-written computer software developed in MATLAB® was used for the detection of ECG R-peaks, and systolic blood pressure. Parabolic fitting was used to detect ECG R-peaks, where a parabola of a length based on the sampling frequency of ECG signal is fitted around the R-wave to determine R-wave maximum. The R-R time series, obtained from the time intervals between consecutive R-peaks, were visually scanned for artefacts and, if necessary, manually edited. Systolic blood pressure (SBP) was determined as the peak magnitudes of the continuous blood pressure signal between two consecutive R-peaks.

2.4. Derivation of respiratory signal

Frank ECG orthogonal XYZ leads signals (derived from 12-leads using Dower's inverse transform) were used to derive respiratory signal using a recent method presented by Lazaro et al. [7]. For each QRS complex, two slopes were measured: the upward slope of the R-wave and the downward slope of the R-wave. From the sample point associated with maximum slope, a straight line of 8ms interval is fitted to each side of the R-wave. The slopes of the line are the required QRS slopes. The smallest angle formed by the two fitted straight lines is defined as the R-wave angle. The calculations of QRS slopes and R-wave angle are illustrated in figure 1 (top panel). By adding the series of either QRS slopes or R-wave angle associated with the occurrence of each beat, an unevenly sampled respiratory signal was obtained. This signal was then interpolated at 4Hz using cubic-splines interpolation technique to obtain an evenly sampled ECG-derived respiratory signal, as shown in figure 1 (bottom panel). The phases of the respiratory signal were calculated using the Hilbert transform.

2.5. Joint symbolic dynamics approach

For the alignment of R-R time series to SBP time series, we started from the R-peak following the first SBP to ensure that blood pressure mediated baroreflex control of heart rate is reflected in our analysis [5]. From the vectors of R-R time series, SBP and respiratory phases, RP (taken at the instants of R-peaks), we established three symbolic sequences, s^{HR} (HR denoting the heart rate—reciprocal of R-R interval), s^{SBP} and s^{RP}, using the transformation rule below that is based on the differences between successive R-R intervals, SBP and R-instant respiratory phases, respectively, as described previously [3].

$$s_i^{HR} = \begin{cases} 0 \text{ if } RR_{i+1} - RR_i > 0 \\ 1 \text{ if } RR_{i+1} - RR_i \le 0 \end{cases} \quad (1)$$

$$s_i^{SBP} = \begin{cases} 0 \text{ if } SBP_{i+1} - SBP_i \le 0 \\ 1 \text{ if } SBP_{i+1} - SBP_i > 0 \end{cases} \quad (2)$$

$$s_i^{RP} = \begin{cases} 0 \text{ if } |RP_{i+1}| - |RP_i| > 0 \\ 1 \text{ if } |RP_{i+1}| - |RP_i| \le 0 \end{cases} \quad (3)$$

Subsequently, series of words, w^{HR}, w^{SBP} and w^{RP} of length two were constructed. Consequently, four different word types were obtained for each vector.

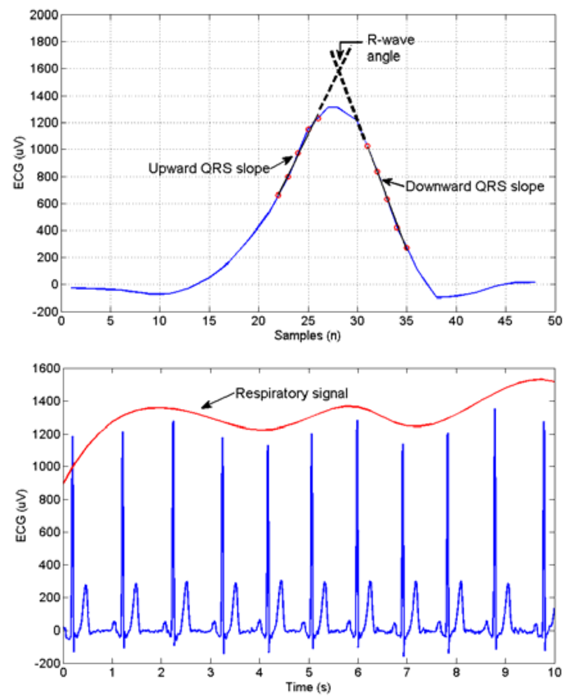

Figure 1. Derivation of respiratory signal from orthogonal ECG. Calculation of QRS slopes and R-wave angle is shown in top panel. Bottom panel shows the final evenly sampled derived respiratory signal from the ECG.

The interactions between the signals were studied by comparing each i^{th} (i = 1,2,…,n, where n is total number of words) word from the distributions, w_i^{HR}, w_i^{SBP} and w_i^{RP}. If the sequence of symbols in w_i^{HR} was reversed to that of w_i^{SBP}, it was considered to be a baroreflex pattern. Subsequently, the baroreflex activity was studied for each combination of respiratory phases: inspiratory phase (w_i^{RP}='11'), expiratory phase (w_i^{RP}='00') and transitional phases (w_i^{RP}='01', '10'). The word types span over a 4×4×4 matrix from $[00,00,00]^T$ to $[11,11,11]^T$ (Table 1).

Table 1. Transformation of RR, SBP and RP into symbol vectors, s^{HR}, s^{SBP} and s^{RP}, and words of length 2, w^{HR}, w^{SBP} and w^{RP}, respectively. The star indicates baroreflex activity during expiratory phase while the plus indicates baroreflex activity during inspiratory phase.

RR

730	690	710	695	687	700	690	685

s^{HR}

	1	0	1	1	0	1	1
w^{HR}:	-	10	01	11	10	01	11

SBP

106	110	108	115	122	118	123	128

s^{SBP}

	1	0	1	1	0	1	1
w^{SBP}:	-	10	01	11	10	01	11

|RP|

1.89	1.21	0.43	1.71	2.92	2.35	1.18	0.15

s^{RP}

	1	1	0	1	0	1	1
w^{RP}:	-	11	10	01	10	01	11

w^{HR}	w^{SBP}				w^{RP}
	00	***01***	***10***	***11***	
00				*	***00***
01			*		
10		*			
11	*				
…					***01***
…					***10***
00				+	***11***
01			+		
10		+			
11	+				

For baroreflex pattern analysis, the combinations of words between w_i^{HR} and w_i^{SBP} that represent baroreflex activity were considered and their occurrence in each respiratory word type (i.e. phase) was studied. The percentage of baroreflex activity (%baroreflex) for each word type of respiratory phases was determined; %baroreflex was calculated by dividing the total count of a particular word pattern representing baroreflex activity by the total count of all baroreflex word patterns.

2.6. Statistical analysis

GraphPad Prism version 6.05 for Windows (GraphPad Software, San Diego, California, USA) was used for statistical analysis. Percentages of baroreflex activity (%baroreflex) were log-transformed to achieve normal distribution of data across the respiratory phase patterns. We investigated changes in baroreflex activity between different respiratory phases using repeated measures ANOVA. For post-hoc analysis, Tukey's multiple comparison test was used. Values with $p < 0.05$ were considered statistically significant. Data were expressed as mean ± standard deviation (SD).

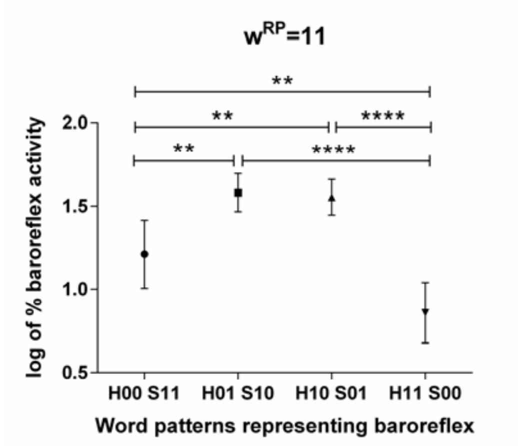

Figure 2. Analysis of the relationship between different patterns of baroreflex response during inspiration. A strong association between word patterns of baroreflex activity was observed. Here, ** and **** represents $p < 0.01$ and $p < 0.0001$ respectively, '00','01', '10' and '11' represent different word types.

3. Results

3.1. Inter-relationship between respiratory phase pattern and baroreflex activity

The mean R-R interval of the subjects was 903±93 ms. Baroreflex patterns were more frequent during inspiratory phase (98.9±2.3%) as compared to expiratory and transitional phases; thus baroreflex activities at inspiratory phases were considered for further analysis.

3.2. Comparison of baroreflex patterns during inspiratory phase

The baroreflex patterns with alternating low-high/high-low SBP and heart rate (w_i^{SBP}=01/10, w_i^{HR}=10/01) were significantly more frequent as compared to continuous increase/decrease in SBP and heart rate (w_i^{SBP}=00/11, w_i^{HR}=11/00) as shown in figure 2; for example, (w_i^{SBP}=10,w_i^{HR}=01,w^{RP}=11: 39.1±9.3% vs. w_i^{SBP}=00,w_i^{HR}=11,w^{RP}=11: 6.4±3.9%, p<0.0001). However, there were no significant differences in baroreflex activity between NYHA class I-II and class III participants (figure 3).

4. Discussion

To our knowledge, this is the first paper to investigate inter-relationship between respiratory phase and baroreflex activity using JSD in heart failure patients. Our results indicate that in these patients baroreflex patterns are mostly observed during inspiratory phase. In addition, baroreflex activity generated from alternating pattern changes in heart rate and SBP was observed to be significantly higher compared to baroreflex with continuous increase or decrease in heart rate and SBP, which may indicate cardiac impairment.

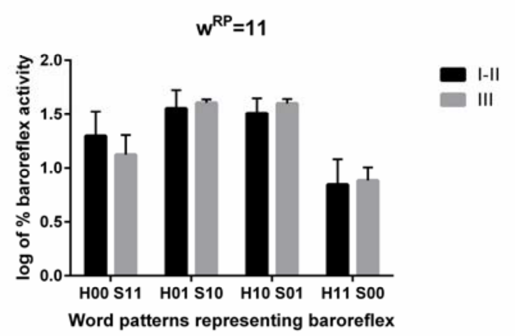

Figure 3. Comparison of log-transformed percentage of baroreflex activity for different baroreflex word patterns between participants with NYHA class I-II and NYHA class III. No significant differences between the two groups were observed.

Respiratory sinus arrhythmia is modulated by vagal tone, and blunted heart rate variability (HRV) and blunted baroreflex are associated with increased mortality after myocardial infarction (MI). The quantification of HRV for predefined sections of the respiratory cycle improves risk stratification of post-MI death. Bivariate phase-rectified signal averaging method has been developed and showed a strong association between expiration-triggered shortening of RR intervals and death after MI [8].

Beat-to-beat variations with a repetitive alternation of measurement parameters such as heart rate and blood pressure are considered to be important in the functional assessments of patients. It has been reported that in patients suffering from dilated cardiomyopathy, short-term alternations of heart rate and blood pressure were significantly higher compared to healthy controls [6]. The beat-to-beat oscillation between lower and higher levels of blood pressure can be observed in clinical states of heart failure [6], which supports our finding of a higher baroreflex activity in the presence of systematic short-term alternations in SBP and heart rate.

Previous studies evaluated each component of cardiorespiratory dynamics in isolation. Importantly, our study for the first time conducted joint analysis of the beat-to-beat variability in RR' intervals, blood pressure, and respiration in heart failure patients. We showed that heart failure patients with advanced degree of mechanical dyssynchrony are characterized by high amount of baroreflex patterns with short-term alternations in SBP and heart rate during inspiration. Further investigation is necessary to understand the inter-relation between respiration and baroreflex activity in heart failure patients.

5. Conclusion

The approach based on joint symbolic dynamics provides an efficient technique for the combined study of respiration-baroreflex activity. Analysis of baroreflex patterns arising from short-term alternations in SBP and heart rate during inspiratory phases may have diagnostic impact on the assessment of heart failure patients.

Acknowledgements

The authors would like to thank CNSystems Medizintechnik AG for providing CNAP Monitor 500. Cohort study is supported by Medtronic, Inc as physician-initiated project (PI Tereshchenko).

References

[1] Gates GJ, Mateika SE, Basner RC, Mateika JH. Baroreflex sensitivity in nonapneic snorers and control subjects before and after nasal continuous positive airway pressure. Chest 2004;126:801-7.

[2] Baumert M, Baier V, Truebner S, Schirdewan A, Voss A. Short- and long-term joint symbolic dynamics of heart rate and blood pressure in dilated cardiomyopathy. IEEE Trans Biomed Eng 2005;52:2112-5.

[3] Kabir MM, Saint DA, Nalivaiko E, Abbott D, Voss A, Baumert M. Quantification of cardiorespiratory interactions based on joint symbolic dynamics. Ann Biomed Eng 2011;39:2604-14.

[4] Caminal P, Vallverdu M, Giraldo B, Benito S, Vazquez G, Voss A. Optimized symbolic dynamics approach for the analysis of the respiratory pattern. IEEE Trans Biomed Eng 2005;52:1832-9.

[5] Baumert M, Javorka M, Kabir MM. Joint symbolic analyses of heart rate, blood pressure and respiratory dynamics. J Electrocardiol 2013;46:569-73.

[6] Leder U, Pohl H-P, Baier V, Baumert M, Liehr M, Haueisen J, Voss A, Figulla HR. Alternans of blood pressure and heart rate in dilated cardiomyopathy. PACE 2002;25:1307-14.

[7] Lazaro J, Alcaine A, Romero D, Gil E, Laguna P, Pueyo E, Bailon R. Electrocardiogram derived respiratory rate from QRS slopes and R-wave angle. Ann Biomed Eng 2014;40:2072-83.

[8] Bauer A, Morley-Davies A, Barthel P, Muller A, Ulm K, Malik M, Schmidt G. Bivariate phase-rectified signal averaging for assessment of spontaneous baroreflex sensitivity: pilot study of the technology. J Electrocardiol 2010;43:649-53.

Address for correspondence.

Muammar M. Kabir
Knight Cardiovascular Institute,
Oregon Health and Science University.
Portland, OR 97239, USA
Email: kabir@ohsu.edu