Effect of Resistive Inspiratory and Expiratory Loading on Cardio-Respiratory Interaction in Healthy Subjects

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***Abstract*— Resistive loading affects the breathing pattern and causes an increase in negative intrathoracic pressure. The aim of this paper was to study the influence inspiratory and expiratory loading on cardio-respiratory interaction. We recorded electrocardiogram (ECG) and respiratory inductance plethysmogram (RIP) in 11 healthy male subjects under normal and resistive loading conditions. The R-R time series were extracted from the ECG and respiratory phases were calculated from the ribcage and abdominal RIP using the Hilbert transform. Both the series were transformed into ternary symbol vectors based on the changes between two successive R-R intervals or respiratory phases, respectively. Subsequently, words of length '3 digits' were formed and the correspondence between words of the two series was determined to quantify cardio-respiratory interaction. Adding inspiratory and expiratory resistive loads resulted in an increase in inspiratory and expiatory time, respectively. Furthermore, we observed a significant increase in cardio-respiratory interaction during inspiratory resistive loading as compared to expiratory resistive loading (ribcage: 22.1±7.2 vs. 12.5±4.3 %, *p*<0.0001; abdomen: 18.8±8.5 vs. 12.1±3.1 %, *p*<0.05, respectively). Further studies may aid in better understanding the underlying physiological mechanisms and management of patients with breathing disorders.**

I. Introduction

It is well known that breathing under resistive loading causes a change in breathing pattern, resulting in an increase in respiratory period, tidal volume and intrathoracic pressure [1-3]. Additional resistance in the respiratory system also increases arterial baroreceptor stimulation within the respiratory cycle [4, 5]. Changes in respiratory pattern are known to influence respiratory related changes in heart rate and heart rate variability [6].

Cardio-respiratory interaction is a concept derived from nonlinear systems theory that aims to quantify the interaction between heart rhythm and respiration, assuming they are generated by two independent systems [7]. Cardio-respiratory response to resistive loading have been investigated in previous studies using fixed-pace breathing [4] and applying resistive loads throughout the entire breathing cycle [8]. To our knowledge, this is the first study to investigate the effect of independent inspiratory and expiratory resistive loading on cardio-respiratory interaction.

Quantification of cardio-respiratory interaction has several clinical merits, such as stratifying the risk of cardiac death in patients after myocardial infarction [9] and diagnosing obstructive sleep apnea [10]. Understanding of cardio-respiratory response to resistive loading may elucidate pathways underlying the development of cardiovascular disorders in patients with breathing problems such as sleep apnea. However, the analysis of cardio-respiratory interaction is difficult since cardiac and respiratory signals are inherently non-linear, non-stationary and contaminated with noise. Conventional signal-processing techniques such as cross-correlation analysis and power spectral density appear to be inadequate for characterizing the complex dynamics of these signals. In a recent study, we proposed a technique based on joint symbolic dynamics of respiratory phase and heart rate for the quantification of cardio-respiratory interaction [11]. The concept of symbolic dynamics employs a coarse-graining procedure in which some of the detailed information is lost but the robust properties of the dynamics are preserved, and therefore provides an easy interpretation of physiological data through a simplified description by means of a few symbols [12-14].

In this paper we applied our proposed approach based on joint symbolic dynamics to quantify and analyse cardio-respiratory interaction during resistive inspiratory and expiratory loading. We hypothesized that cardio-respiratory interaction is perturbed by resistive loading.

II. Methods

A. Subjects

Eleven male healthy subjects recruited from among the undergraduate students participated in this study. The age of the subjects ranged between 19 and 25 years. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Human Research Ethics Review Board of the University of Adelaide. Informed consent was obtained from all subjects.

B. Experimental protocol

The experiment was conducted in the supine position. Subjects were allowed to breathe through a custom-made T-

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TABLE I
ILLUSTRATION OF THE TRANSFORMATION OF R-R INTERVALS (RR) AND RESPIRATORY PHASES (RP) INTO SYMBOL VECTORS, s^{HR} AND s^{RP}, AND WORDS, w^{HR} AND w^{RP}, OF LENGTH 3, AND PLACING THE WORDS IN A 27×27 TABLE MATRIX.

RR (s)

0.67	0.71	0.69	0.73	0.74	0.75	0.73	0.71

s^{HR}

0	1	0	0	0	1	1

w^{HR}: - - 010 100 000 001 011

|RP|

1.87	1.19	1.37	1.69	2.01	2.33	1.16	0.13

s^{RP}

1	0	0	0	0	1	1

w^{RP}: - - 100 000 000 001 011

w^{RP}	w^{HR}						
	000	001	010	011	100	-	-	222
000	*				+			
001		*						
010								
011				*				
100			+					
-								
-								
222								

The '*' indicates that sequence of symbols in w^{HR} corresponds to w^{RP} and hence is considered coordinated. The '+' indicates the pair of words with a difference in sequence of symbols.

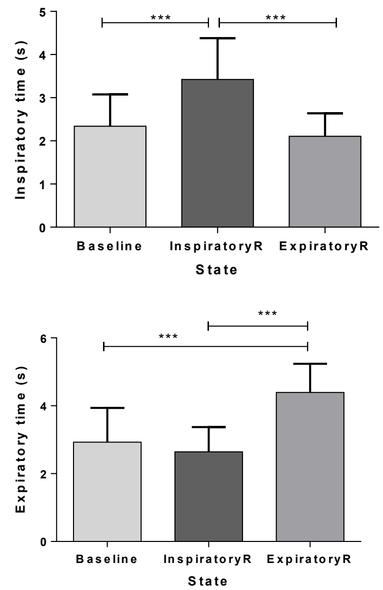

Figure 1. Changes in inspiratory and expiratory time (mean ± SD) during baseline and resistive loading. In the figure, InspirationR and ExpirationR represents resistive load at inspiration and expiration respectively. Here, *** represents $p < 0.0001$.

shaped mouthpiece only. In each subject, three recordings of 10 min duration each were obtained, with no resistive loading or in the presence of a resistance applied to either inspiration or expiration throughout the entire breathing process.

The respiratory movements of the ribcage and abdominal wall, recorded simultaneously using respiratory inductive plethysmography, and the ECG (leads I and II) were sampled at 1 kHz and recorded using PowerLab data acquisition system and ChartPro 6.0 software (ADInstruments, Sydney, Australia). For data analysis, custom written computer program was developed in MATLAB® using the signal processing toolbox.

Two ends of the T-shaped mouthpiece were fitted with one-way air valve to allow unidirectional inhalation and exhalation (controlled by inspiration and expiration; one valve opens and the other closes on inspiration, and vice versa on expiration). Resistive loading was created by blocking either the inhalation or the exhalation end of the T-tube with a cork fitted with straw to allow air in or out. Mouth pressure was measured using a differential pressure transducer. The system was calibrated for each subject before the start of the experiment.

C. ECG and respiratory signal analysis

The ECG R-peaks were detected using parabolic fitting, where a curve was fitted around the R-wave to determine the prominent peak. From the time-stamps of the R-peaks, the R-R time series were extracted and visually scanned for artifacts and, if necessary, manually edited.

Abdominal and chest respiratory signals were low-pass filtered at 0.5 Hz using a zero-phase forward and reverse digital filter. The inspiratory and expiratory onsets, used to compute the breath-to-breath time series, were determined as the zero-crossings of the first derivative of the respiratory signal. Subsequently, the Hilbert transform was used to calculate the phases of the respiratory signal.

D. Joint symbolic dynamics

For the study of cardio-respiratory interaction, the respiratory phases (RP) at the instants of R-peaks were extracted. Using the transformation rule below and based on the differences between successive R-R intervals and R-instant respiratory phases, we established two symbolic sequences, s^{HR} (HR denoting the heart rate—reciprocal of R-R interval) and s^{RP}, from the vectors of the R-R time series and RP, respectively, as described previously [11]

$$s_i^{HR} = \begin{cases} 0 \text{ if } RR_{i+1} - RR_i > 0.004 \\ 1 \text{ if } RR_{i+1} - RR_i < -0.004 \\ 2 \text{ otherwise} \end{cases} \quad (1)$$

$$s_i^{RP} = \begin{cases} 0 \text{ if } |RP_{i+1}| - |RP_i| > 0 \\ 1 \text{ if } |RP_{i+1}| - |RP_i| < 0 \\ 2 \text{ if } |RP_{i+1}| - |RP_i| = 0 \end{cases} \quad (2)$$

From the symbol vectors s^{HR} and s^{RP}, series of words, w^{HR} and w^{RP} of length three (containing three successive symbols) were constructed. In this study, a threshold value of

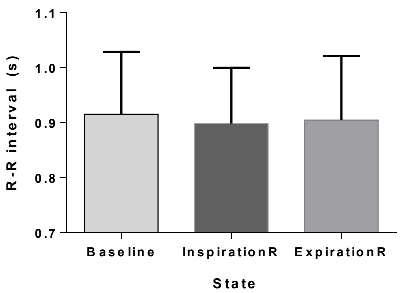

Figure 2. Changes in R-R interval (mean ± SD) during baseline and resistive loading. In the figure, InspirationR and ExpirationR represents resistive load at inspiration and expiration respectively.

0.004 s for s_i^{HR} and words of length '3 digits' were chosen, since they provided more consistent and significant results as determined by the procedure described previously [11]. Consequently, 27 different word types were obtained for each vector. The word types span over a 27×27 vector matrix from $[000,000]^T$ to $[222,222]^T$, as shown in Table I.

In order to study the interaction between cardiac and respiratory cycles, each i^{th} (i = 1,2,…,n, where n is total number of words) word from the distributions, w_i^{HR} and w_i^{RP} was compared against each other. The cardiac and respiratory epochs were considered to be coordinated only if the sequence of symbols in w_i^{HR} was identical to that of w_i^{RP} (i.e. $w_i^{HR} = w_i^{RP}$). The percentage of interaction was calculated by dividing the total count of coordinated words by the total number of words.

E. Statistical analysis

For statistical analysis, GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) was used. We investigated changes in RR interval, respiratory timings and cardio-respiratory interaction between normal and resistive breathing using non-parametric repeated measure analysis of variance. For post-hoc analysis, Dunn's multiple comparison test was used. Values with $p < 0.05$ were considered statistically significant. Data were expressed as mean ± standard deviation (SD).

III. RESULTS

A. Effect of resistive loading on respiratory and R-R intervals

As expected, there was a significant increase in inspiratory time during inspiratory resistive loading as compared to expiratory resistive loading (3.4±1.0 vs. 2.1±0.5 s, p<0.0001), see Figure 1. Similarly, a significant increase in expiratory time was observed during expiratory resistive loading as compared to inspiratory resistive loading (4.4±0.8 vs. 2.6±0.7 s, p<0.0001), see Figure 1. However, no significant changes in R-R interval between normal and resistive loading were observed (Figure 2).

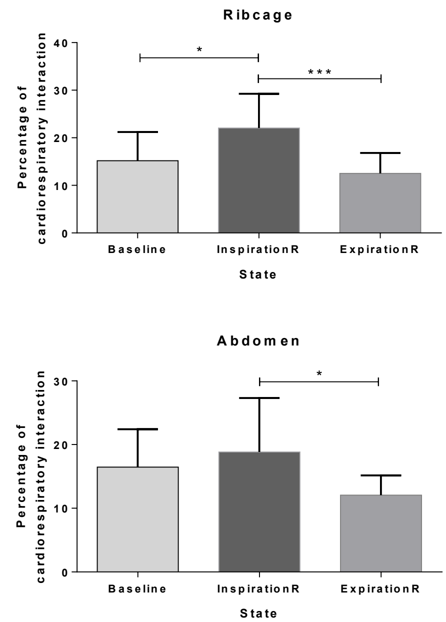

Figure 3. Cardio-respiratory response (mean ± SD) to baseline and resistive loading. In the figure, InspirationR and ExpirationR represents resistive load at inspiration and expiration respectively. A significant increase in cardio-respiratory interaction was observed during inspiratory resistive loading as compared to expiratory resistive loading (ribcage and abdomen). Here, * and *** represent $p < 0.05$ and $p < 0.0001$, respectively.

B. Effect of resistive loading on cardio-respiratory interaction

A significant increase in cardio-respiratory interaction was observed during inspiratory resistive loading as compared to expiratory resistive loading (ribcage: 22.1±7.2 vs. 12.5±4.3 %, p<0.0001; abdomen: 18.8±8.5 vs. 12.1±3.1 %, p<0.05, respectively), see Figure 3. Furthermore, the interaction between ribcage respiratory signal and cardiac rhythms was significantly higher during resistive inspiratory breathing compared to normal baseline breathing (22.1±7.2 vs. 15.2±6.0 %, p<0.05), see Figure 3.

IV. DISCUSSION

In this paper we investigated cardio-respiratory interaction during normal and resistive inspiratory and expiratory loading, using an approach based on joint symbolic dynamics. Our results show that the amount of interaction between the cardiac and respiratory oscillators significantly increased in the presence of a resistance during inhalation as compared to exhalation.

Previously, it has been suggested that analysis of cardiac and respiratory data using symbolic dynamics provide improved performance compared to time-domain analyses [11, 15]. In contrast to previous studies using several parameters for transforming a time series into symbols [15], our proposed methodology described previously [11] and used in this paper involves only two parameters and is based on the changes in consecutive respiratory phases corresponding to the changes in R-R intervals.

In this study we found no significant changes in R-R interval between normal and inspiratory or expiratory resistive breathing, which is similar to the finding by Calabrese *et al.* using resistive loads throughout the entire breathing cycle [8].

From the analysis of the interaction between R-R intervals and respiratory phases during resistive loading, a significant increase in cardio-respiratory interaction was observed in the presence of resistance during inhalation as compared to exhalation. According to Seals *et al.*, the addition of a resistance to inspiratory breathing cycle would highly increase the negative intrathoracic pressure during voluntary inspiration at any given lung volume [5]. It has also been noted that muscle sympathetic nerve activity was inhibited during inspiration during breathing with added inspiratory resistance, despite a fall in arterial blood pressure [5]. This would suggest that the decrease in sympathetic nervous activity (and presumably a relatively higher vagal outflow) during inspiratory resistive loading was responsible for the increase in cardio-respiratory interaction, which is in line with one of our previous studies in rats [16].

Obstructive breathing is known to increase asynchrony between ribcage and abdominal respiratory signals [17]. The change in ribcage-abdominal coordination is possibly due to the greater respiratory effort required to overcome the loading resistance. Nevertheless, the effect of inspiratory resistive loading on cardio-respiratory interaction was observed in both the signals.

According to recent studies, respiratory timing, variability and respiratory related changes in heart rate are affected in patients with sleep disordered breathing [18, 19]. Consequently, this study has clinical significance and can be used to better understand the underlying physiological mechanisms. Further studies using larger group of subjects (healthy controls and patients) and longer recordings with advanced resistive-load controlling device are required to determine whether the changes in cardio-respiratory interaction are particularly due to resistive loading effects or there are other factors involved such as the influence of central neuronal processes in the brain controlling reflex actions.

V. Conclusion

This paper illustrated a simple technique for the study of the interaction between cardiac and respiratory cycles under resistive independent inspiratory and expiratory loading. According to our analysis, cardio-respiratory interaction is perturbed by the changes in breathing patterns caused by resistive inspiratory loading. Further studies may aid in understanding and management of patients with breathing disorders.

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