Respiratory Physiology & Neurobiology 189 (2013) 27–33

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Respiration and heart rate complexity: Effects of age and gender assessed by band-limited transfer entropy

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ARTICLE INFO

Article history:
Accepted 20 June 2013

Keywords:
Heart rate variability
Respiratory sinus arrhythmia
Aging
Entropy

ABSTRACT

Aging and disease are accompanied with a reduction of complex variability in the temporal patterns of heart rate. This reduction has been attributed to a break down of the underlying regulatory feedback mechanisms that maintain a homeodynamic state. Previous work has established the utility of entropy as an index of disorder, for quantification of changes in heart rate complexity. However, questions remain regarding the origin of heart rate complexity and the mechanisms involved in its reduction with aging and disease. In this work we use a newly developed technique based on the concept of band-limited transfer entropy to assess the aging-related changes in contribution of respiration and blood pressure to entropy of heart rate at different frequency bands. Noninvasive measurements of heart beat interval, respiration, and systolic blood pressure were recorded from 20 young (21–34 years) and 20 older (68–85 years) healthy adults. Band-limited transfer entropy analysis revealed a reduction in high-frequency contribution of respiration to heart rate complexity ($p < 0.001$) with normal aging, particularly in men. These results have the potential for dissecting the relative contributions of respiration and blood pressure-related reflexes to heart rate complexity and their degeneration with normal aging.

1. Introduction

Although it is known that aging is associated with increased cardiovascular risk (Lakatta et al., 2009; Najjar et al., 2005; Ryan et al., 1994; Shiogai et al., 2010), the underlying mechanisms are poorly understood. Furthermore, diseases such as obstructive sleep apnea, which are independent risk factors for cardiovascular disease, increase in prevalence with age (Ancoli-Israel et al., 1996; Wellman et al., 2007; Young et al., 2002), and may contribute to overall cardiovascular risk. In order to assess the relationships between age and cardiovascular control, investigators have used indices of heart rate (HR) variability (based on the variance of HR time series) and complexity (based on predictability and nonlinear relationships in HR time series), with most studies demonstrating a reduction in HR variability and complexity with age (Goldberger et al., 2002; Nolan et al., 1998; Ponikowski et al., 1997; Tsuji et al., 1996). However, the specific mechanisms for this reduction are not known.

There are a number of mechanisms that contribute to variability in HR; among them are those linked to variability in blood pressure and respiration (including periodic and aperiodic oscillations). They may emerge as a result of various delayed feedback and feedforward pathways between the system variables (Bruce, 1996; deBoer et al., 1987; Nemati et al., 2011), as well as the influence of signals from the afferent and efferent nerves influencing vagal-cardiac motoneuron and pacemaker cells involved in generation of heart beat and respiration (Del Negro and Hayes, 2008; Eckberg, 2009). Quantification of the coupling between HR and factors such as blood pressure and respiration is therefore necessary to probe the origin of the reduction in HR variability and complexity with age. Using spectral analysis of HR and respiration, several authors have shown a significant reduction with age in HR variability in the frequency ranges associated with breathing (Pinna et al., 2006; Singh et al., 2006). However, techniques using spectral analysis make major assumptions about the underlying system dynamics including linearity and stationarity. Such limitations are important given that previous research has suggested that the coupling between respiration and cardiovascular system is strongly nonlinear (Novak et al., 1993; Wessel et al., 2009), and in this case, spectral analysis is not appropriate.

Given these limitations, Goldberger et al. have successfully used techniques from nonlinear dynamics, such as fractal scaling and entropy, to characterize subjects according to the nonlinear

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http://dx.doi.org/10.1016/j.resp.2013.06.016

complexity of their HR (Goldberger et al., 2002; Iyengar et al., 1996; Lipsitz and Goldberger, 1992; Ryan et al., 1994). The concept of *entropy* for assessing higher order temporal structures in the time series has been emphasized (Ryan et al., 1994; Takahashi et al., 2012), since it does not make any assumptions about the linearity of the system. Notably, a conditional variant of entropy known as *sample entropy* has been widely used to assess the complexity of HR (Humeau et al., 2008; Lake et al., 2002; Moorman et al., 2011; Vaillancourt et al., 2004). By extension, *multiscale entropy*, which examines the entropy at different time-scales, has been suggested as an effective tool to assess physiological systems (Costa et al., 2002). However, a limitation of all these techniques (including spectral methods when applicable) is that they do not assess directional relationships (e.g., the nonlinear influences of respiration and blood pressure on HR), and therefore, without substantial prior physiological knowledge, have limited power to reveal the underlying mechanisms responsible for the changes in complexity.

As such the major aim of the current work is to develop a technique based on the concept of *band-limited transfer entropy* to quantify the contribution of both respiration and blood pressure to HR complexity over multiple frequency bands. The proposed technique aims to track the directional coupling between both respiration and blood pressure with HR over low and high frequency bands, which are influenced by the sympathetic and parasympathetic regulatory reflexes (Robinson et al., 1966; Shannon et al., 1987). Previously, Iyengar et al. (1996) demonstrated a reduction in complex variability of HR (based on the concept of fractal scaling) with aging in a subset of subjects from the Physionet Fantasia database. Here we confirm the findings of that study within the entire Fantasia dataset (Goldberger et al., 2000) using a conditional entropy analysis, and then assess the aging-related changes in contribution of respiration and blood pressure to HR complexity within the male and female populations using the technique of band-limited transfer entropy.

2. Methods

2.1. Dataset

Our cohort consisted of a group of healthy subjects from the *Physionet Fantasia* database (Goldberger et al., 2000; Iyengar et al., 1996), which consisted of 20 young subjects (21–34 years) and 20 older adults (68–85 years). Each group was made up of equal numbers of males ($n = 10$) and females ($n = 10$). The subjects underwent two hours of continuous monitoring in supine resting position while watching the Disney movie 'Fantasia'. Continuous time-synchronized measurements of electrocardiogram (ECG) and respiration (impedance plethysmography) were collected in all subjects. Additionally, non-invasive measurements of blood pressure (tonometric pressure, Colin Electronics) were recorded in a subset of 10 young and 10 older adults. All waveforms were recorded at 250 Hz sampling frequency. All of our analyses are limited to artifact-free segments of the data, determined according to the signal quality assessment procedure described below.

2.2. Preprocessing and extraction of beat-by-beat time series

An example of the processed waveforms and time series is shown in Fig. 1. We used the automatically detected, visually verified and corrected ECG R-peak annotations available on the Fantasia website (Goldberger et al., 2000) to derive time series of peak-to-peak (RR) intervals. Within each RR interval, a search was performed to find the location of peaks of the blood pressure; these constituted our systolic blood pressure (SBP) time series. The onset of each breath was detected as follows (Nemati et al., 2011). We first removed the baseline drift (often seen in impedance plethysmography-based measurement of respiratory volume) by fitting a cubic spline function through all the breath onsets, and subtracting the resulting "baseline" curve from the respiratory waveform; the resulting volume waveform started at zero upon the onset of each breath. Next, we constructed a respiratory volume time series for each RR interval from the volume difference at the times of the R wave peaks (see Fig. 2, panels A, C, and E).

Due to the presence of artifacts in ECG and blood pressure waveforms, we also calculated indices of waveform signal quality via constructing template (or average) beats and assigning a signal quality index (SQI) to every ECG and blood pressure beat according to their correlation coefficient with their corresponding templates; where a correlation coefficient near unity represents a high quality signal. For each subject, a separate template beat for ECG and blood pressure was constructed by placing a temporal window of size equal to median RR interval (symmetric around the waveform peaks) on each beat and averaging the windows over all the beats. Next, each record was segmented into continuous artifact-free blocks of ECG (and when available blood pressure) with SQIs of larger than 0.7. Finally, all samples within each time series were replaced with their ranks (similar to nonparametric statistical tests) (Lee et al., 2012) in order to eliminate the problem of data outliers while still preserving all the joint information among time series (Darbellay and Vajda, 1999; Hudson, 2006b). We used the resulting time series within all the artifact-free data blocks for the estimation of transfer entropy.

2.3. Transfer entropy

Recent techniques for studying nonlinear directional relationships among discretized physiological variables have been based on utilizing the concept of *transfer entropy* (Lee et al., 2012; Porta et al., 2011). Briefly, given two time series $X = \{x_1, x_2, \ldots, x_N\}$ and $Y = \{y_1, y_2, \ldots, y_N\}$, the transfer entropy from X to Y, denoted $T_{X\to Y}$ (Lee et al., 2012) is defined by:

$$T_{X\to Y} = H(y_i|y_{i-1}) - H(y_i|y_{i-1}, x_{i-\tau}), \quad (1)$$

where for an arbitrary time series Z with probability density $P(z_i)$, its entropy $H(Z) = -\sum_{z_i} P(z_i)\log P(z_i)$ is related to the amount of information needed to predict the future values of the time series. Thus, a time series with a high level of entropy tends to be more random and have greater complexity. Furthermore, the *conditional entropy* term $H(z_i|z_{i-\tau}) = \sum_{z_i, z_{i-1}} P(z_i, z_{i-\tau})\log(P(z_{i-\tau})/P(z_i, z_{i-\tau}))$, where $P(z_i, z_{i-\tau})$ is the joint probability density, is the amount of information needed to predict the future values of Z if we know its past value at some lag τ. For example, the conditional entropy of RR intervals, denoted as $H(\mathrm{RR}_i|\mathrm{RR}_{i-1})$, is the amount of information needed to predict the future value of RR given that we know its current value at time i. Thus in Eq. (1), the transfer entropy from X to Y, $T_{X\to Y}$, quantifies the amount the history of X at lag τ (i.e., $x_{i-\tau}$) predicts the current value of Y (i.e., y_i) beyond the amount it is already predicted by its own immediate history (i.e., y_{i-1}). When considering the transfer entropy from both SBP and RESP to RR intervals, we varied the lag parameter τ from 1 to 6, and we report the lag with the maximal transfer entropy. The fast parasympathetic (or vagal) responses allow the SBP and RESP to affect RR interval within one beat, while the slower sympathetic response may take two or three beats to attain its maximal effect (deBoer et al., 1987; Eckberg, 2009).

Calculation of the conditional entropy quantities in Eq. (1) requires estimation of joint probability distributions among the variables of interest. Typically this procedure is done by binning the data in a manner similar to constructing histograms, which requires an often arbitrary decision regarding the number and size of bins. In