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Impact of respiration on cardiovascular coupling using Granger causality analysis in healthy subjects

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ABSTRACT

This quantitative study delineates the influence of respiratory rate on cardiovascular signal in healthy subjects using granger causality approach. Electrocardiogram (*RR*), arterial blood pressure (*SBP*) and respiration (*RESP*) were simultaneously recorded for 5 min from 20 subjects during normal (13–20 cycles/min) and deep breathing (5 cycles/min) with equal inspiration and expiration time. During deep breathing mean *RR* remains same but the variance increases. Also deep breathing lowers blood pressure, increases baroreflex sensitivity and improves oxygen saturation. The traditional frequency domain methods based power spectrum analysis and coherence analysis lacks to measure coupling changes among physiological subsystems. Therefore, frequency domain Granger causality method based on directed coherence is proposed to detect the changes in coupling strength among cardiovascular signals under different respiration rates. Directed coherence spectrum can separate *RESP*, *SBP* and *RR* components from each recorded signals. The *RESP* component of both *RR* (RR_{RESP}) and *SBP* (SBP_{RESP}) increases (coherence > 0.5) significantly during deep breathing indicate that respiration affects both cardiac and vascular system but at normal breathing only cardiac system (RR_{RESP}) get affected by respiration. Also a significant increase in coherence is observed on baroreflex direction (RR_{SBP}) indicating that deep breathing controls blood pressure. Hence, the observed directed coherence spectrum helps to detect coupling changes among cardiac, vascular and respiratory signal during autonomic regulation.

1. Introduction

The cardiovascular coupling is depicted as a closed loop system with mechanical feed forward and baroreflex feed back. The impact of blood pressure on heart rate variability is identified as arterial baroreflex control and its converse produces mechanical feed-forward mechanisms [1]. Baroreflex is responsible for regulating blood pressure at constant value irrespective of heart rate variation. The increased heart rate elicits an increase in blood pressure and activates baroreflex that opposes the increased heart rate. The impact of respiration on heart rate can be obtained from respiratory sinus arrhythmia (RSA), inspiration increases heart rate while expiration decreases heart rate. The loss of RSA is linked with cardiac mortality [2]. On the other hand, inspiration decreases blood pressure and expiration increases blood pressure [3]. Therefore, the study of respiration effect on cardiovascular system is found significant [4,5]. Several studies identified the effect of respiration on cardiovascular system [6–8].

To identify the cardiovascular changes spectrum analysis [9] is found as an accurate method. The spectral analysis calculates power spectral density (PSD) at different frequency bands [10–14] mainly at low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz) to comprehend different physiological mechanisms responsible for the autonomic regulation of cardiovascular system [15–17]. From previous literature, LF represents both sympathetic (mainly blood pressure variability at 0.1 Hz Mayer waves) and parasympathetic nerve activity but HF represents mainly parasympathetic nerve activity (respiratory effect) [18]. When respiration rate is more than 9 cycles/min, respiration frequency is in HF range and is mediated by parasympathetic nerve system. But when respiration rate reduces below 9 cycles/min then respiration frequency shifted to LF range [19]. The controlling of breathing at a reduced respiration rate on healthy subject is obtained using deep breathing technique. Deep breathing increases variability of heart rate and controls blood pressure [10].

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Since spectral analysis is univariate analysis so it cannot detect the coupling changes among systems. To detect coupling between the systems, bivariate analysis based on cross-correlation and coherence analysis is normally used. These bivariate coupling analyses lack to detect the coupling changes occurring on multivariate system. Therefore to detect multivariate coupling changes, Granger causality has been found as a preferred method for evaluation of coupling, i.e., of directional interaction. Granger causality approach identifies causal interaction from one time series to another. It provides linear prediction about the behavior of time series from its past by incorporating direct and indirect influences [20]. To comprehend the effect of one system on another, the cause–effect (coupling) relation within and between the systems have to be considered. Scientific literatures based on Granger causality analysis on cardiac and neural signals are found noteworthy [21–23]. Several coupling techniques based on Granger causality have been developed to detect and quantify the direct and indirect coupling changes of multivariate systems [21,24,25]. In this study directed coherence (DC) approach based on frequency domain Granger causality analysis is utilized to detect the changes in causal coupling during deep breathing [25]. This DC is quantified using coherence values for each interaction. As interaction or coupling between systems increases coherence value increases and for completely interacted system the coherence value will be one.

This frequency domain Granger causality is first proposed by Akaike [26] and further named as DC analysis [27] and is based on multivariate autoregressive modeling (MVAR). MVAR modeling provides paramount importance in the description of multivariate time series [28–30]. DC quantifies interaction by calculating the amount of the cross-spectral density between time series [12]. DC can be applied to both bivariate and multivariate time series. DC is derived as a factor of ordinary coherence analysis. In cardiovascular analysis, the DC spectrum is helpful to identify the link between their oscillatory components. The directed coherence value is calculated at LF and HF bands to individually understand the effect of each system on another.

The cardiovascular system works in synchronous with respiratory system. The variation in cardiovascular coupling during respiration is non-identifiable directly therefore to identify them respiration rate have to change. In particular, it is also not known how cardiovascular coupling changes during deep breathing. In this study normal breathing (13–20 cycles/min) and deep breathing (5 cycles/min) is performed to determine whether the changes in respiration rate produce an impact on cardiovascular coupling or not. The DC calculated among cardiac, vascular and respiratory signal determines the changes in the direction and strength of coupling during deep breathing. The obtained directed coherence power spectrum is compared with standard spectrum analysis using PSD.

2. Materials and method

2.1. Experimental data

Ten minutes recordings were made from 20 healthy young subjects (8 females and 12 males of age 26 ± 4 are selected in order to nullify sex related changes) in supine position, which were free from diseases that can affect autonomic function. The selected subjects are not practicing any kind of breathing exercise or yoga from 6 months. The subjects were instructed not to use any medicine at least 24 h before recording and also no consumption of tea or food stuff, at least, 3 h before the recording. The recording is done in quiet room with comfortable light and temperature levels. All procedures performed in human participants were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5) and an informed consent also taken from all subjects that included in the study. The recording uses Biopac MP100 system attached with ECG lead, NIBP 100B (FUSION) non-invasive blood pressure monitor and respiratory belt. The acquired ECG, arterial blood pressure and respiratory flow are digitized at 1000 Hz sampling rate (f_s) with 12-bit precision and is given in Fig. 1. ECG (in mV) obtains from Einthoven's triangle Lead II configuration. The blood pressure (in mmHg) sensor of NIBP 100B (FUSION) non-invasive blood pressure monitor estimates the pressure in the radial artery at the wrist. Respiratory flow (in mV) is obtained using respiratory effort transducer belt that measures the changes in abdominal circumference.

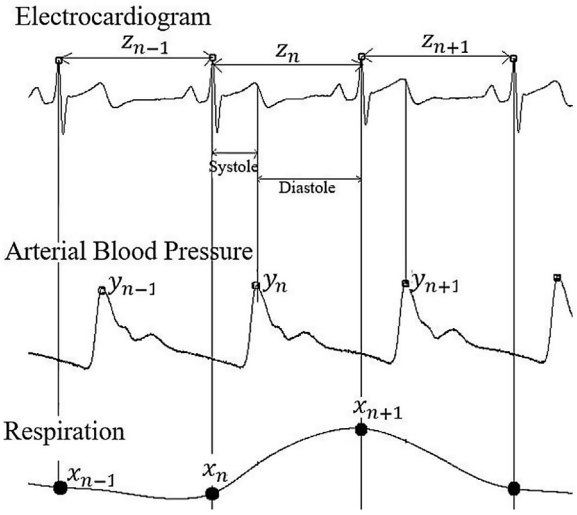

Fig. 1. Original recorded signal where z_n, y_n and x_n represent electrocardiogram, arterial blood pressure and respiration respectively.

Recording is done for 5 min in normal breathing (range of 13–20 cycles/min, 0.2–0.3 Hz frequency) and further 5 min in deep breathing (5 cycles/min, 0.08 Hz frequency). The instruction for inhaling and exhaling during deep breathing at regular interval (with 6-s inspiration and 6-s expiration) is given by an instructor. For cardiovascular stabilization, 1-min resting period is provided between two consecutive recordings.

2.2. Extraction of beat to beat RR, SBP and RESP time series

ECG, arterial blood pressure and the respiratory flow signals were preprocessed to remove noise due to power line interference (50 Hz), muscle movements, etc. ECG R-peaks are detected using Tompkins's algorithm [31] and systolic blood pressure (*SBP*) peaks from [32]. From the detected R-peak of ECG signal, beat-to-beat variability series is extracted and is given by *RR* interval. Respiratory peak (*RESP*) is the amplitude of the respiratory signal taken at the onset of detected ECG R-peak. Specifically, the *n*th *RR* was identified from the ECG as the temporal interval and denoted as z_n The corresponding *SBP* and *RESP* values, denoted as y_n and x_n, were measured respectively as the maximum of the blood pressure signal inside the *n*th *RR* interval, and as the amplitude of the respiratory signal taken at the onset of the *n*th *RR* interval. The subsequent data analysis is performed for normal and deep breathing of each subject. Three hundred simultaneous samples of *RR*, *SBP* and *RESP* were considered for analysis and represented in Fig. 2 of a representative subject. The obtained time series are then normalized by subtracting its mean and dividing by standard deviation (SD).