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Feasibility study for the assessment of cardio-respiratory coupling in newborn infants

Maristella Lucchini,

Dipartimento di Elettronica, Informazione e Bioingegneria (DEIB), Politecnico di Milano, Italy

William P. Fifer,

Department of Psychiatry, Columbia University College of Physicians & Surgeons, New York, NY 10032, USA.

Manuela Ferrario [Member EMBS], and

Dipartimento di Elettronica, Informazione e Bioingegneria (DEIB), Politecnico di Milano, Italy

Maria G. Signorini [Member EMBS]

Dipartimento di Elettronica, Informazione e Bioingegneria (DEIB), Politecnico di Milano, Italy

Abstract

Cardio Respiratory Coupling (CRC) plays a key role during infant development. Nonetheless, mechanisms underlying it are still mostly unexplained and tools to assess it are often inadequate to understand its functioning. This study aims to evaluate the feasibility of CRC activity detection and quantification analyzing ECG and respiration of newborn healthy subjects. Cross-spectral analysis (coherence) and a novel application of a nonlinear method (Bivariate Phase Rectified Signal Averaging) were applied on 10 minutes recording from 4 subjects. Our preliminary results show that these methods can provide significant information about the occurrence and the strength of CRC, opening interesting perspectives in the evaluation of cardiorespiratory pathologies in newborn infants. In particular, the observed dynamic behavior appears stable and centered around one single frequency in Quiet Sleep, while being more variable and less consistent in Active Sleep.

I. Introduction

Cardiac and respiratory activities show complex interactions in adults and have been long studied both from a physiological point of view and with mathematical models. Mechanical effects of respiration on modulation of the heart rate (HR) are well known. A primary mechanism is the respiratory sinus arrhythmia (RSA) i.e. the modulation of cardiac vagal efferent activity by the central respiratory drive and the lung inflation reflex. The degree of RSA increases with cardiac vagal activity and it can explain for instance both the shortening of the R-R interval during inspiration and its prolongation during expiration [1], [2].

CRC is crucial to maintain ideal gas exchange and to respond to variable physiological demands. During the first months of life CRC still needs to fully develop and stabilize, since after the transition from fetal to neonatal life the respiratory neural control system needs to

adapt to the extra utero condition. For instance, most preterm infants exhibit recurrent apnea, resulting in repetitive oscillations in O_2 saturation [3]. This event affects the respiratory activity, which is unstable within the same subject and not comparable among newborns. Moreover, even in full-term newborn infants altered respiratory frequency may lead to a decrease modulation of HR variability (HRV) [4]. It has been also shown that CRC strength during sleep increases in the first 6 months of life, suggesting that this mechanisms is part of the developmental steps of neonatal life [5].

Interestingly, some studies proposed an altered CRC as a key aspect in the onset of Sudden Infant Death Syndrome (SIDS), such as an inadequate response to hypoxic and hypercapnic challenges [6], or inverse CRC leading to a life- threatening event [7].

Both time domain and frequency domain methods, such as standard spectral analysis [8], have been proposed to quantify CRC and in particular to evaluate RSA. Mathematical methods have been developed including also breath-by-breath analysis for the assessment of HRV [9].

However, all these approaches assume that signals are stationary or quasi-stationary within the considered time windows, which is a valid assumption in adults for limited period of time, especially during sleep. This is not always the case in newborns, whose behavioral states continuously change over time (e.g. sleep/awake alternation, position changes) [10].

The main purpose of this paper is to assess the strength of CRC in healthy full-term newborns and to test the feasibility and reliability in detecting CRC and its physiological changes over short period of observation. To reach this goal, we considered both the frequency coherence estimation and the bivariate phase-rectified signal averaging (PRSA) to investigate the cardiorespiratory system.

II. Materials and Methods

A. Patients and data collection

For this pilot study, we identified 4 newborns born at 40 weeks. They were selected from a larger cohort of 308 healthy subjects based on the length and the quality of the data. All babies were recorded in supine position to limit confounding factors. ECG and Respiratory activity were recorded non-invasively, at a sampling rate of 500 Hz and 20 Hz respectively, by means of three leads on the chest and by a chest belt. These signals were acquired at Columbia University Medical Center. Approval of the Ethical Committee of the hospital was obtained prior the acquisitions.

During acquisition, babies sleep states were classified into Active Sleep (AS) and Quiet Sleep (QS). Two babies were classified as in AS while two in QS. Recording time was about 10 minutes.

RR series were detected on the ECG by applying the Pan-Tompkins algorithm. An adaptive filter was then applied to remove ectopic beats or artifacts [11]. Respiratory Phase (inspiration/expiration) was assessed by applying the Hilbert transform to the respiratory signal.

B. Cardiorespiratory coupling analysis

The RR series and the respiratory signal were resampled at 5 Hz by applying a cubic spline. Each 10 minute segment was analyzed by considering overlapping moving windows of 3 minutes shifted of 1 minute each.

In order to assess an adaptive threshold for the coherence function between RR and Respiration rate, 100 surrogate series were generated according to the Schreiber algorithm, Iterative Amplitude Adjusted Fourier Transform, as fully described in [12], [13] thus preserving the signal ACF. For each pair of surrogate series, the coherence $k^2(f)$ was estimated and for each frequency bin its empirical sampling distribution was computed.

Successively, the threshold was defined as the 95th percentile of the coherence value sampling distribution. The threshold was applied for frequencies ranging from 0.35 Hz to 1.45 Hz, i.e. in the physiological range generally be related to the respiratory activity in newborns.

Coherence was computed by applying the Welch averaged modified periodogram method, considering 1-minute segments overlapped at 50% and windowed with Parzen window.

The values obtained from the coherence in the original series were compared to the estimated threshold. If these values passed the threshold for three consecutive frequency bins, those frequencies were considered as linearly correlated. In this case, the delay between the two time series was estimated: given ϕ as the median value of the phases in correspondence of such frequencies, the delay (τ) was estimated as $-\phi / 2\pi f$ where f is the mean of those frequencies.

C. Bivariate phase-rectified signal averaging (PRSA)

The univariate PRSA technique aims at studying quasi-periodic oscillations and nonlinear effects in non-stationary signals. The Bivariate PRSA (BPRSA) is a generalization of the previous method, aiming at highlighting interrelationships between two signals supposed synchronous, defined as a trigger and a target signal [14], [15]. The BPRSA algorithm consists in 3 major steps:

- Detection of anchor points (APs). APs are defined as increments (or decrements) in the trigger signal. Increments are estimated on series averaged every T samples. The choice of T can be optimized depending on the frequency of interest, according to this empirical relationship $T=1/(2.5 \cdot F)$. The APs are used to identify the corresponding samples on the target signals.
- The identification of all the time windows of length $2L$ ($=50$ samples) around each AP by considering L samples before and L samples after the AP.
- Averaging of all $2L$ windows.

The median of the frequency values that correspond to coherence values above the threshold was used to estimate T , which typically ranges from 0.2 to 0.8 seconds.

Univariate PRSA was estimated for the Respiratory Phase; the method is the same with target and trigger signals that are the same time series. The delay between the RR and respiratory series was estimated as the difference between the central peak of the PRSA curve of the Respiratory Phase and the BPRSA, as suggested in [15].

Few of the advantages of PRSA are that it does not assume stationarity and it claim to be less affected by data quality than traditional methods. Moreover, BPRSA transforms the target signal in a compressed version, maintaining only (quasi)periodicities that are coupled to the trigger signal, eliminating uncoupled periodicities, artifacts, or noise.

Comparing the BPRSA transformation of the target signal with the monovariate PRSA transformation of the trigger signal is possible to observe possible trigger and target signal interaction.

III. Results

Figure 2 shows three different patterns of respiratory frequency in three different subjects: panel 2(a) shows a recording in QS with a clear respiratory peak frequency, panel 2(b) shows the spectrum of a baby in AS with two possible respiratory peak frequencies and panel 2(c) the spectrum of a baby in AS with a wide range of frequencies.

Figure 2 shows the coherence matrices corresponding to the spectra in figure 2. Figure 3(a) shows a clear CRC centered around 0.6–0.7 Hz that is constant for the entire recording. CRC in Figure 3(b) is associated to two different frequencies which may correspond to the two main breathing frequencies seen in figure 2(b). In Figure 3(c) there is no clear and constant coupling throughout the recording. Delay estimation between the two signals (τ) was obtained from the Phase Spectrum (Table I).

For the BPRSA, the Respiratory Phase was used as the trigger signal whereas RR series as the target. Moreover, APs were analyzed both as increments and decrements in the Respiratory Phase.

Figure 3 illustrated two examples. In the upper panels a clear entrainment is visible whereas the lower panels show a weak CRC. In the first case, the median CRC frequency was estimated as 0.62 Hz, and $T=3$ samples (0.6 seconds), in the second case the median CRC frequency was 0.89 Hz, with corresponding value of $T=2$ samples (0.4 seconds). Values of the estimated delays are summarized in Table 1.

IV. Discussion and Conclusion

In literature, several methods have been proposed to quantify the coupling between cardiac and respiratory activity, including traditional cross-spectral analysis. In this paper we propose an application of this latter method in combination with a novel application of a nonlinear approach called BPRSA to verify the occurrence and the strength of CRC in newborn infants.

The analysis highlighted different characteristics in CRC according to the sleep state considered. Firstly, during QS (Subject 1 and 2) a consistent coupling around an individual central frequency throughout the ten minutes was observed. During AS (Subject 3 and 4), the coupling was less marked and not always evident for the entire recording. This suggests that sleep state affects the CRC and the variability of the respiratory frequency, and this is line with previous results [16].

BPRSA can provide an estimate of the delay between Respiratory Activity and RR series oscillations. As figure 4 shows, the curve of BPRSA is sensitive to CRC, extracting periodic interrelated behaviors, often masked by resetting due to internal and external perturbations. This nonlinear approach is the strength and the novelty of BPRSA in comparison with traditional approaches, including coherence.

No clear difference was observed comparing increment APs or decrement APs during each recording, and this hints that the regularity of respiratory frequency plays a greater role than the value itself of the frequency. In terms of time delay, the 4 subjects did not present the same values. However in QS, the two babies present positive delay for both increment APs and decrement APs, meaning BPRSA peak occurring before Respiratory Phase PRSA peak. This did not happen for the babies in AS, suggesting a different coupling. Previous results presented by Bauer et al. [15], showed that in adult typically the increase in Respiratory Phase PRSA was always preceding BPRSA by one beat, indicating a more stable CRC than in newborn.

In the next future, this same approach will be applied to a larger cohort so to consider also the within subject variability, i.e. the same baby in the two different conditions (AS and QS).

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Figure 1:

The spectra of the Respiratory Phase for (a) subject 1 window 7, (b) subject 3 window 1, (c) subject 4 window 1. The spectra of Subject 2 are similar to that of subject 1

Figure 2:

The heat maps refer to the recordings in Figure 2. They are constructed by assigning 1 when the coherence function exceeds the threshold estimated with the surrogate techniques (purple boxes) and 0 elsewhere (green boxes)

Figure 3:

the curve of PRSA of respiratory phase signal is in blue, the curve of BPRSA is in green, the upper panel refers to increment APs, the lower panel to decrement APs (a) Subject 1 with a clear and synchronous coupling (b) Subject 4, with a weak CRC.

Table 1

Indices values calculated for each subject in each time moving window

Condition	Indices	W1	W2	W3	W4	W5	W6	W7
Sub. 1	Mean RR (sec)	0.472	0.475	0.474	0.471	0.465	0.465	0.465
	k ² in resp. band	0.693	0.741	0.783	0.791	0.721	0.754	0.778
	Time delay (τ) (sec)	-1.02	0.10	0.075	1.23	1.21	0.101	-0.98
	PRSA $\uparrow$ time delay (sec)	0	0	0	0	0	0	0
	PRSA $\downarrow$ time delay (sec)	0	0	0	0	0.2	0.2	0.2
Sub. 2	Mean RR (sec)	0.525	0.521	0.519	0.517	0.516	0.510	0.504
	k ² in resp. band	0.729	0.695	0.6795	0.768	0.788	0.811	0.739
	Time delay (τ) (sec)	0.24	0.26	0.23	0.22	1.34	0.22	0.26
	PRSA $\uparrow$ time delay (sec)	0.2	0.2	0.4	0.2	0.2	0.2	0.2
	PRSA $\downarrow$ time delay (sec)	0.6	0.4	0.4	0.4	0.4	0.4	0.4
Sub. 3	Mean RR (sec)	0.483	0.475	0.472	0.473	0.475	0.483	0.486
	k ² in resp. band	0.669	0.670	0.748	0.6898	0.700	0.6917	0.635
	Time delay (τ) (sec)	-0.33	1.88	0.59	1.871	1.87	1.84	0.76
	PRSA $\uparrow$ time delay (sec)	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4	-0.4
	PRSA $\downarrow$ time delay (sec)	0.6	0.6	0.6	0.8	0.8	0.8	0.8
Sub. 4	Mean RR (sec)	0.418	0.417	0.420	0.423	0.426	0.425	0.422
	k ² in resp. band	0.577	0.622	0.626	0.587	0.589	0.617	0.615
	Time delay (τ) (sec)	0.84	1.73	-2.563	0.683	-1.50	0.92	0.792
	PRSA $\uparrow$ time delay (sec)	-0.2	-0.2	-0.4	-0.4	-0.4	-0.4	-0.4
	PRSA $\downarrow$ time delay (sec)	0.6	0.6	0.6	0.6	0.6	0.6	0.8