Interdependence in the Cardiorespiratory Network of Preterm Infants with Pulmonary Hypertension using Mutual Information Analysis

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Abstract

Aim: Immature development predisposes preterm infants to cardiorespiratory morbidities such as pulmonary hypertension (PH) and bronchopulmonary dysplasia (BPD). This study investigated interdependence in the cardiorespiratory network and identified differences exhibited by infants with BPD alone and those with the added complication of PH.

Methods: Heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2) from 17 infants with BPD alone (NoPH group) and 21 infants with BPD and PH (PH group) were analyzed using mutual information (MI). MI over varying time delays between pairs of signals were estimated and the maximum value, mxMI, if significant, was extracted and compared between groups.

Results: Interdependence differed based on condition and coupling signals. Within groups, MI(HR-SpO2) was strongest while HR-RR had the smallest magnitude dependence. HR-SpO_2 coupling in the PH group was higher than in the NoPH group ($p<0.001$). The shortest mean delay occurred in the HR-RR interaction.

Conclusion: Cardiorespiratory interaction strengths were altered in preterm infants with both BPD and PH. Information transfer between cardiorespiratory network components in preterm infants may hence provide insights to mechanisms of disease progression and needs to be explored further.

1. Introduction

Preterm infants are vulnerable to many morbidities among which Bronchopulmonary dysplasia (BPD) is highly prevalent [1]. Arising mainly from immature development of the lungs, the progression and management of this disease is further complicated by Pulmonary hypertension (PH), which increases infants' risks of mortality [2–4]. Hence, early detection of PH is recommended for preterm infants [5].

Oxygen desaturation known as intermittent/severe hypoxemia has been implicated in evolving BPD and PH [6], and these events are often observed concomitantly with other adverse events such as apneas and bradycardias [7]. The exact nature of the interaction between these systems is however not yet completely understood in infants [8].

Cardiorespiratory interactions in neonates have been assessed, especially during sleep and have been related to maturational changes [9, 10]. Physiological signals from the cardiorespiratory network were analyzed using methods drawn from information-theory, causality analysis and network science to provide insights into the functional dependence of these systems. In preterm infants with BPD, a third important component in this interactive network is the oxygen saturation in the blood. Hence, our aim was to investigate the interdependence between these – the cardiac, respiratory, and pulmonary systems - in infants with BPD. We hypothesized that significant interdependence of oxygen saturation with the respiratory and cardiac components will be detected and there may be differential coupling behavior exhibited by infants with only BPD and those having both BPD and PH, due to the physiological changes attributable to disease severity in the latter group.

2. Methods

2.1. Subjects and Data

Heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2) data were prospectively collected in extremely preterm infants admitted at the University of Alabama at Birmingham (UAB) between 2018 and 2020 as part of the Prematurity-Related Ventilatory Control (Pre-Vent) study, with approvals and oversights by IRB-UAB and a board appointed by the NHLBI. Approval from the institutional review board was obtained for physiological and clinical data collection with waiver of consent.

Bedside cardiorespiratory monitoring was carried out by Philips IntelliVue MP70 or MP50 monitors using Nellcor pulse oximetry sensors, an averaging time of 8 s, and recorded using the BedMaster system (Excel Medical

Electronics, Jupiter FL, USA) at 125 Hz with data analyzed using numeric data at 1 Hz. 21 infants with BPD and PH (BPD-PH group) diagnosed by echocardiography were included in the study, along with 17 infants with BPD without PH (NoPH group).

Two hours of data from each subject were segmented into non-overlapping ten-minute windows. These segments were pre-processed to remove artefactual values that can occur due to recording errors, sudden movements etc. Missing data gaps of less than 10 seconds were imputed by the average value of the vital sign over the previous three seconds. Segments with total missing data of more than 2% of their length were excluded.

2.2. Mutual Information as an interdependence measure

Mutual Information (MI), a metric derived from information theory has found application in various fields of study in biomedical science and medicine [11–13] . It quantifies the information gained about one random event from observations of another [14] and measures the linear and nonlinear dependencies existing between the two sets of data.

Consider $X = \{x_i\}$ and $Y = \{y_j\}$ representing two sets of random observations with probability distribution of amplitudes given by $P_X(x_i)$ and $P_Y(y_j)$, respectively. The mutual information (MI) between X and Y quantifies the reduction in the uncertainty of X by measurements made on Y and is given as

$$MI(X,Y) = H(X) - H(X|Y) \qquad (1)$$

where $H(X)$ is the average information gained from measurements of X, and $H(X|Y)$ is the mean conditional uncertainty in measuring X under the condition that Y is known.

By incorporating time lagged variables, the dynamic mutual information between two time series can be estimated as,

$$MI(X(t), Y(t+\tau) = \sum_{(x_t, y_{t+\tau})} P_{X,Y_\tau}(x(t), y(+\tau)) \log\left(\frac{P_{X,Y_\tau}(x(t), y(t+\tau))}{P_X(x(t)) P_{Y_\tau}(y(t+\tau))}\right) \qquad (2)$$

Estimation of the joint probability distribution from finite sized data collected in biomedical settings is a challenge. Many methods to estimate these distributions and subsequently MI, exist in the literature [15]. In this study, we employed the k nearest neighbour approach that is recommended for use with short biomedical data sets [16] and its MATLAB implementation for estimating the MI [17]. The time delay between pairs of signals varied from -15 to 15 seconds and MI was estimated at each of these values.

2.3. Statistical Validation and Modelling

The significance of the estimated MI values relative to the null hypothesis of independence between two series was determined. This was achieved by aggregating a bootstrap null distribution of the test statistic estimated from surrogates of the original series as given in [18]. We created 100 time-shifted surrogates of one signal of a pair and determined the MI between these and the original second signal to compile the null distribution. If the MI between the original pair of signals was within 95% of the surrogate MI values, it was considered as significant.

The maximum significant MI value and the time delay at which it occurred for each set of interactions in each segment were noted as mx_MI and τ respectively. Two-way ANOVA analyses were performed on these measures with factors CONDITION (2 levels – BPD-NoPH, BPD-PH) and COUPLING PAIRS (3 levels: HR-RR, HR-SpO_2, RR- SpO_2). In cases where significant main effects were found, post-hoc tests with Tukey-Kramer correction for multiple comparison were conducted. $P < 0.05$ indicated significance in all cases.

3. Results

3.1. Estimation of MI measures

Each subject initially contributed 12 ten-minute segments of each type of physiological data for analysis.

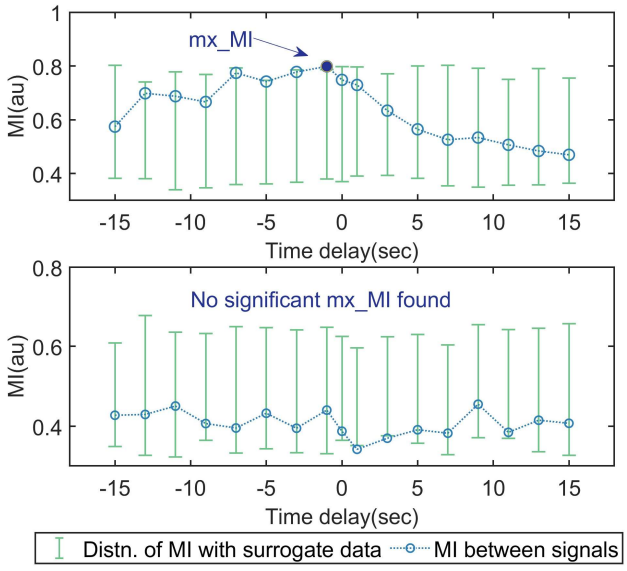

Figure 1. MI indices estimated over multiple time delays for two pairs of HR and RR segments from a subject. At each time delay, the MI values obtained from surrogate data are also shown by the error bars. In the top panel, the statistically significant maximum MI is marked.

Hence, the No-PH group had 204 segments of data while 252 segments were available for analysis in the BPD-PH group. Signal loss or missing data caused a few of these segments to be excluded. For the remaining segments, the MI was estimated over delay times ranging between pairs of signals and the maximum value determined, based on the independence test compared to the surrogate data values. This procedure is shown in Figure 1 for two cases, one in which the mx_MI was significant and the other where no interdependence could be detected for two segments from the HR and RR series.

Finally, from the No-PH group, 78%, 69% and 73% segments had admissible MI values in the HR-RR, HR-SpO_2 and RR-SpO_2 coupling scenarios. Accordingly, these were 73%, 67% and 58% for infants in the BPD-PH group.

3.2. Analysis of interdependence measures

The interdependence values, mx_MI and the corresponding delay times, τ are represented as boxplots in Figures (2) and (3) along with results from the ANOVA modelling. The central line in the boxplots represents the median value with the edges representing the first and third quartiles. The solid dots represent the averages in each case. The whiskers extend from the median to 1.5 times the interquartile range. The values beyond this are marked as outliers (dots) in both figures.

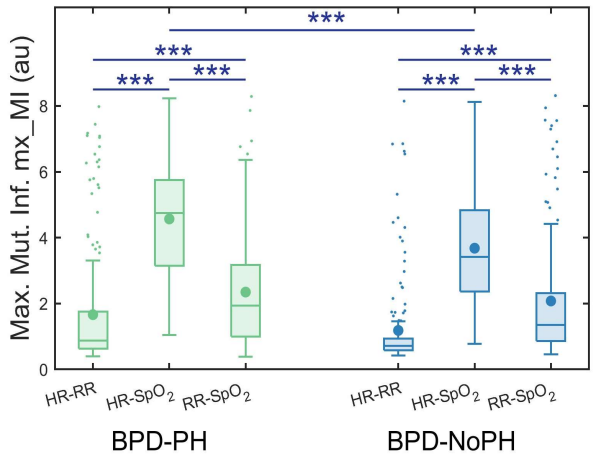

Figure 2. Maximum mutual information for couplings between vital signs for each infant group.
*** p<0.001

The maximum mutual information estimated from the pairs of signals and the delay time corresponding to it were analysed by performing two-way ANOVA to model the effect of having PH (CONDITION) and different pairs of signals (COUPLING PAIRS) on the interdependence.

The results for mx_MI indicated a significant main effect for CONDITION, F (1,941) = 25, p <0.001; a significant main effect for COUPLING PAIRS, F (2, 941) = 219.4, p<0.001; and an insignificant interaction between these effects, $F(2,941)$ = 2.66, p = 0.07. Multiple comparison tests indicated that mx_MI was higher in the BPD-PH group compared with NoPH group and within each CONDITION the interdependences were different between pairs of signals.

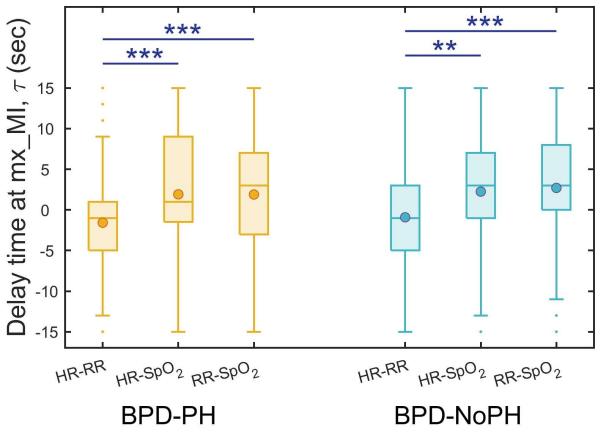

Figure 3. Boxplot of delay time corresponding to the maximum mutual information for couplings between vital signs for each infant group. *** p<0.001

A similar analysis for the delay times revealed a significant effect only for COUPLING PAIRS, F (2, 941) = 24.7, p<0.001; and insignificant effects for both the CONDITION, F (1,941) = 1.6, p = 0.2 and interaction between these effects, $F(2,941)$ = 0.08, p = 0.92. Multiple comparison between delay times within subject groups showed significantly higher values for interdependence pairs involving SpO_2 compared to that of HR-RR coupling.

4. Discussion

In this study, the interdependence existing in the cardiorespiratory network of preterm infants was investigated using measures of mutual information between the heart rate, respiratory rate, and oxygen saturation levels. These infants were all diagnosed with BPD, a serious lung condition, while a subgroup also had the added complication of pulmonary hypertension (PH). The analysis identified that the interdependence between HR and SpO_2 was higher in the BPD-PH group. Within groups, this coupling showed the highest interdependence while the weakest coupling was between HR and RR.

The pattern in interaction strengths, quantified by mutual information between the signals was the same in both infant groups, indicating that underlying influences between the cardiac, respiratory, and pulmonary systems

may be the same for these infants who all had underlying BPD.

However, the HR-SpO_2 interdependence was observed to be significantly stronger in infants with PH and BPD, compared with their counterparts who had BPD alone. This implied that information transfer between cardiac and oxygenation components was greater in infants with PH. The average time scale over which this occurred was the same for both groups, about 2 seconds, implying a non-contemporaneous interaction, with previous HR values correlating strongly with present oxygenation levels. Within infant groups, the delay times of the HR-RR interaction was found to be significantly faster than the interactions involving SpO_2.

Infants in the BPD-PH group also exhibited greater independence between the network components, though this needs to be investigated further. Independence was detected in cases where the maximum MI failed to reject the null hypothesis via surrogate analysis. Although not tested statistically, interaction of SpO_2 with RR was found to be independent for 42% of the segments in the PH group compared with 27% in the No-PH group.

The duration of intermittent hypoxemia or oxygen desaturations has been reported to be longer in infants with PH and has been proposed as a potential bedside marker of the progression of this disease [6]. Hypoxemia events have also been associated with occurrence of respiratory apneas and bradycardias, making oxygen saturation an important component in studying the cardiorespiratory network of pre-term infants with BPD [19].

Our findings in this preliminary study support the hypothesis that physiological signals may impact each other differently due to the presence of PH in addition to BPD. How these dependencies change when a segment contains an adverse hypoxemia event and whether causal relationships can be derived by use of other measures such as transfer entropy will be the future directions of this work.

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