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Quantification of cardiovascular and cardiorespiratory coupling during hypoxia with Joint Symbolic Dynamics

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Abstract—**Newborn mammals suffering from moderate hypoxia during or after birth are able to compensate a transitory lack of oxygen by adaptation of their vital functions. However, limited information is available about bivariate couplings of the underlying complex processes controlled by the autonomic nervous system. In this study an animal model of seven newborn piglets (2-3 days old, 1.71±0.15 kg) was used. The aim of this study was to analyze the cardiovascular and cardiorespiratory interactions of autonomous nervous system during sustained hypoxia and the interrelationship of these autonomic time series after induced reoxygenation. For this purpose we applied a new high resolution version of the nonlinear method of Joint Symbolic Dynamics (JSD) for analysis of couplings between heart rate and blood pressure and respiration rate time series, respectively. This new method is characterized by using three defined symbols (JSD3) instead of two and the application of thresholds for the symbol transformation. Our results demonstrate that in contrast to the traditional JSD the comparison of cardiovascular interactions reveals only significant differences between normoxic and hypoxic conditions using JSD3 whereas for cardiorespiratory interactions significant differences were revealed by indices from both JSD2 and JSD3 due to reoxygenation. These results suggest that the application of JSD3 reveals more detailed information about cardiovascular and cardiorespiratory interactions of autonomic regulation and might be useful for monitoring of critical human newborns.**

I. Introduction

Sustained systemic hypoxia is a common consequence during maladaptation from intrauterine to extrauterine life [1] and may lead to a fatal exit or lifelong severe disabilities in case of progressive oxygen lack [2]. Though, moderate systemic hypoxia of lower degree is compensated by the neonate throughout a prolonged period [3].

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However, there is a lack in knowledge on time- and intensity-related adaptation of autonomic control under moderate hypoxic conditions in the newborn life. The newborn piglet achieves a degree of maturity at birth similar to that of humans in regard to the cardiovascular regulation [4]. Therefore, this species have been considered an excellent sub-primate laboratory model for comparison with human infants.

There is limited information about short-term bivariate dynamics between cardiovascular and respiratory signals that alter during the dynamical development from normoxia to hypoxia and during reoxygenation. The combined analysis of heart rate (HR) and systolic blood pressure (SP) and respiration rate (RESP) time series, respectively, might provide further information about the complex system of autonomic regulation as if these time series are analyzed only univariate. The interrelationship between HR and SP or HR and RESP is to be assumed at least partly nonlinear. Therefore, it seems necessary to apply methods that consider also these nonlinear dynamics.

To characterize these beat-to-beat interactions of HR and SP time series more detailed, the method of Joint Symbolic Dynamics with two symbols (JSD) was recently introduced [5]. JSD allows a simplified quantification of the dynamics of HR and SP with a limited amount of symbols and was successfully applied to heart rate variability (HRV) analysis [6].

To differentiate between noise and fluctuation which arise from autonomic regulation we developed a new high resolution version of JSD introducing three symbols (JSD3), and in addition, a threshold for symbol transformation.

We hypothesize that JSD2 and especially JSD3 indices applied to cardiovascular and respiratory time series can reveal alterations and changes of complexity in autonomic regulation of piglets due to adaptation to hypoxia. Thus, this provides a greater comprehension of temporal and intensity characteristics of autonomic regulation in regard to adaptation of newborns to reduced and re-established oxygen supply. Finally, most important findings of this study should be useful in pediatrics for recognizing and monitoring hypoxic effects that occur in human neonates.

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II. Materials and Methods

A. Animal Data and Preprocessing

Data were used from seven newborn piglets (2-3 days old, 1.71±0.15 kg) enrolled in a previous study to estimate the effect of artificial ventilation on regional blood flow in newborns [7]. The study was approved by the local ethic committee. In the experiment these piglets were anesthetized and could breathe spontaneously under normoxia and normocapnic hypoxia. Initially resting conditions were monitored for 60min (normoxia). After this the inspired fraction of oxygen was reduced from 0.3 to about 0.1 by appropriate exchange with nitrogen, causing a normocapnic hypoxia for approximately 60min. Finally the gas mixture was re-established for recording recovery for 30 min (reoxygenation).

High resolution ECG, synchronized continuously blood pressure and respiration signals (2048Hz sampling frequency, fs) were recorded from all seven subjects. Recording time varied from 137 to 191 minutes. ECG was measured by standard limb leads using needle electrodes (HSE EKA - Puls IC, Hugo Sachs Elektronik K.G.), while respiration waves were recorded by impedance plethysmography on the chest wall (Apnocard 300, Mechanische Werkstätten Radeberg). Aside, one catheter was advanced through an umbilical artery into the abdominal aorta to record arterial blood pressure (P23Db, Statham Instruments Inc.). All time series of beat-to-beat intervals (*BBI*), systolic blood pressure values over time (*SP*) and interval times between consecutive breathing cycles (*RESP*) were extracted automatically by a pattern matching cross correlation and thereafter filtered to remove and interpolate (spline) ventricular premature beats and artifacts by an adaptive filter algorithm to get normal-to-normal beat time series (*NN*) [8]. For cardiorespiratory coupling analyses signals were resampled with a frequency of 4Hz to obtain synchronized time series.

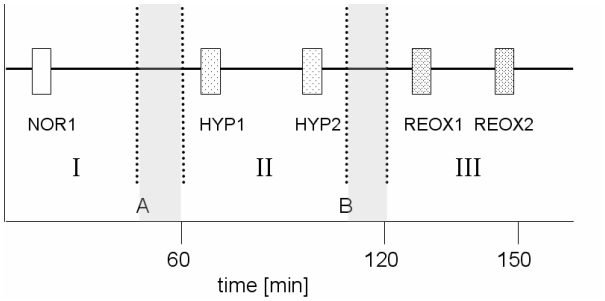

Fig. 1. Schematic sketch of phase extraction from time series for all piglets during normoxia (I), hypoxia (II) and reoxygenation (III): phases NOR1, HYP1, HYP2, REOX1 and REOX2 were chosen for analyses. A: start of hypoxia, B: end of hypoxia, grey boxes: non-stationary transition phases.

Regarding to the extraction of time series for all states from all seven piglets the maximum segment length providing processable qualitative signals was manually checked and remained six minutes. In case of longer usable time series we applied a test, where the extracted time segments fulfilled pre-selection criteria considering stationarity within the investigated data segments. Here, local mean values and standard deviations of shifted windows inside the extracted time segments did not differ more than 5% from global mean values and standard deviations.

Subsequently, the dynamical behavior before, during and after hypoxia was analyzed to quantify the changes of autonomic regulation. For this purpose, one six minute phase from the beginning of normoxia (NOR1) was used for each following comparison with early hypoxia (HYP1), late hypoxia (HYP2), early reoxygenation (REOX1) and late reoxygenation (REOX2) (Fig. 1).

B. Joint Symbolic Dynamics - JSD

X (1) represents a bivariate vector where x^{BBI} and x^{SP} are n beat-to-beat values of BBI and SP, respectively.

$$X = \left\{ \left[x_n^{BBI}, x_n^{SP} \right]^T \right\}_{n=0,1,\ldots} \quad x \in R \tag{1}$$

X is transformed into S (2) defined as

$$S = \left\{ \left[s_n^{BBI}, s_n^{SP} \right]^T \right\}_{n=0,1,\ldots} \quad s \in R \tag{2}$$

with the following definitions:

$$s_n^{BBI} = \begin{cases} 0 : \left(x_n^{BBI} - x_{n+1}^{BBI} \right) \le l^{BBI} \\ 1 : \left(x_n^{BBI} - x_{n+1}^{BBI} \right) > l^{BBI} \end{cases} \tag{3}$$

$$s_n^{SP} = \begin{cases} 0 : \left(x_n^{SP} - x_{n+1}^{SP} \right) \le l^{SP} \\ 1 : \left(x_n^{SP} - x_{n+1}^{SP} \right) > l^{SP} \end{cases} \tag{4}$$

In the traditional JSD $(JSD2)$ method the threshold l was set to zero. Hence, increases between two successive BBI and SP, respectively are coded as "1" and consequently decreases and equilibrium are coded as "0". Afterwards S is subdivided into short sequences w_k of the length k.

The word types are sorted into a 8x8 vector matrix W from $[000,\ 000]^T$ to $[111,111]^T$ [5].

To compromise the word distribution between time series of different length, the sum of all word events is normalized to 1. Using a threshold the problem occurs that the word type $[000,\ 000]$ is the most numerous one and it is not possible to distinguish between decrease and steady state.

Therefore a new high resolution version of the JSD method was introduced using 3 symbols $(JSD3)$ to differentiate between increase, decrease and steady state (5-6).

$$s_n^{BBI} = \begin{cases} 0 : \left(x_n^{BBI} - x_{n+1}^{BBI}\right) < -l^{BBI} \\ 1 : -l^{BBI} \le \left(x_n^{BBI} - x_{n+1}^{BBI}\right) \le l^{BBI} \\ 2 : \left(x_n^{BBI} - x_{n+1}^{BBI}\right) > l^{BBI} \end{cases} \quad (5)$$

$$s_n^{SP} = \begin{cases} 0 : \left(x_n^{SP} - x_{n+1}^{SP}\right) < -l^{SP} \\ 1 : -l^{SP} \le \left(x_n^{SP} - x_{n+1}^{SP}\right) \le l^{SP} \\ 2 : \left(x_n^{SP} - x_{n+1}^{SP}\right) > l^{SP} \end{cases} \quad (6)$$

The word types are sorted into a 27x27 vector matrix W (Fig. 2) ranges from $[000,\ 000]^T$ to $[222,\ 222]^T$.

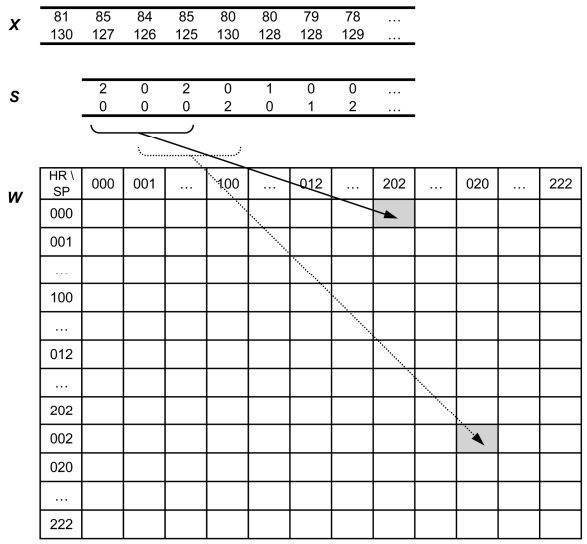

Fig. 2. Transformation of bivariate symbol vector s into the vector matrix W (27x27) – here cardiovascular interaction.

The threshold l was set to different levels of the group standard deviation (25%, 50%, and 100%) and as a reference l was set to zero. The normalized probabilities of all single word types' occurrences, the sum of each column (same *SP* or *RESP* word) and the sum of each row (same *BBI* word) were computed. The parametric t-test was applied for the statistical evaluation of all significant differences in JSD2 and JSD3 indices between the different time segments of the piglet's data. The global significance level was set at p_g = 0.01. To verify the use of the t-test, the Kolmogorov-Smirnov-Test with Lilliefors correction was performed in advance (normal distribution). Descriptive statistics are used to describe the basic features of the data as mean value and standard deviation.

There is a need to adjust for multiple testing when assessing the statistical significance of findings. Therefore, we applied the Bonferroni-Holm method [9] to confirm the t-test results (#). We compared the quantity of significances in applying JSD3 with the occurring significances in that of JSD2.

TABLE 1A. JSD3 CARDIOVASCULAR INDICES FOR DISCRIMINATION BETWEEN NORMOXIA (NOR1), EARLY HYPOXIA (HYP1) AND LATE HYPOXIA (HYP2); JSD – JOINT SYMBOLIC DYNAMICS; * - P < 0.01; ** - P < 0.001; # - SIGNIFICANT AFTER BONFERRONI-HOLM ADJUSTMENT; N.S. – NOT SIGNIFICANT.

method	index	NOR1 vs. HYP1	NOR1 vs. HYP2
JSD3	S002B111	**#	*#
	SBP100	*#	n.s.
	SBP002	**#	*#
	SBP200	*#	*#
	SBP122	*#	n.s.
	SBP220	*#	*#

TABLE 1B. DESCRIPTIVE STATISTICS FOR JSD3 CARDIOVASCULAR INDICES FOR NORMOXIA (NOR1), EARLY HYPOXIA (HYP1) AND LATE HYPOXIA (HYP2) AS MEAN VALUES ± STANDARD DEVIATIONS.

index	NOR1	HYP1	HYP2
S002B111	0.92 ± 0.52	2.6 ± 0.85	2.33 ± 0.99
SBP100	0.77 ± 0.48	2.9 ± 1.71	2.99 ± 2.03
SBP002	0.95 ± 0.49	2.65 ± 0.86	2.36 ± 0.99
SBP200	1.02 ± 0.67	2.64 ± 0.97	2.39 ± 0.89
SBP122	0.40 ± 0.32	1.92 ± 1.23	2.41 ± 1.71
SBP220	0.72 ± 0.45	2.40 ± 1.43	2.39 ± 1.32

TABLE 2A. JSD2 AND JSD3 CARDIORESPIRATORY INDICES FOR DISCRIMINATION BETWEEN NORMOXIA (NOR1), EARLY REOXYGENATION (REOX1) AND LATE REOXYGENATION (REOX2); JSD – JOINT SYMBOLIC DYNAMICS; * - P < 0.01; ** - P < 0.001; # - SIGNIFICANT AFTER BONFERRONI-HOLM ADJUSTMENT; N.S. – NOT SIGNIFICANT.

method	index	NOR1 vs. REOX1	NOR1 vs. REOX2
JSD2	R000B010	*#	n.s.
	R100B011	n.s.	*#
JSD3	R000B001	*#	n.s.
	R000B020	*#	n.s.
	R200B022	n.s.	*#

TABLE 2B. DESCRIPTIVE STATISTICS FOR JSD2 AND JSD3 CARDIORESPIRATORY INDICES FOR NORMOXIA (NOR1), EARLY HYPOXIA (HYP1) AND LATE HYPOXIA (HYP2) AS MEAN VALUES ± STANDARD DEVIATIONS.

index	NOR1	REOX1	REOX2
R000B010	2.21 ± 1.5	5.41 ± 2.26	5.14 ± 2.56
R100B011	0.94 ± 0.33	0.40 ± 0.39	0.32 ± 0.22
R000B001	0.69 ± 0.39	0.16 ± 0.21	0.31 ± 0.46
R000B020	2.03 ± 1.42	5.08 ± 2.17	4.76 ± 2.66
R200B022	0.90 ± 0.35	0.38 ± 0.35	0.31 ± 0.23

III. RESULTS

A. Cardiovascular interactions

Indices from JSD2 revealed no significant differences for cardiovascular interactions in regard to any group test between NOR1 and all other following intervals (results not shown). In contrast, JSD3 showed significantly (p = 0.0006) increased indices (Table 1a and 1b) due to hypoxia. These significant differences are partly diminished during

prolonged hypoxia. No significances were found for group tests between NOR1 and reoxygenation phases by JSD3 either.

B. Cardiorespiratory interactions

In contrast to cardiovascular couplings, significant alterations in cardiorespiratory interactions were shown by indices from both JSD2 and JSD3 methods due to reoxygenation (Table 2a and 2b). Thus, indices from both methods were significantly ($p = 0.008$) changed during reoxygenation. No significances were found for group tests between NOR1 and hypoxia phases for cardiorespiratory interactions. All presented significances were confirmed by the Bonferroni-Holm adjustment.

IV. Discussion

The applied new high resolution method of JSD3 investigates autonomic interactions in a more detailed and complex manner using different thresholds and three symbols for transforming time series in symbol sequences and respectively in word types. This method revealed an optimum way to differentiate between normoxia and hypoxia analyzing couplings between heart rate and blood pressure time series. A highly significant difference between normoxic and hypoxic conditions was only found using JSD3 and not with the standard JSD2 version. Further on, a slight regression in these altered bivariate couplings was found by JSD3 during prolonged moderate hypoxia. That might assume that the new high resolution JSD3 version is more suitable for differentiating between minor random changes and autonomic regulations due to immediately and sustained hypoxia. The significantly increased JSD3 indices point to a higher proportion of specific trends (words) and to less variability in cardiovascular interactions, consequently. This is in accordance to the depressant effect on cardiovascular function caused by increasing hypoxic acidosis [10]. Both methods showed that cardiovascular interactions are already adjusted back to normoxic conditions after reestablishment of oxygen supply.

Regarding to cardiorespiratory interactions both JSD methods showed similar results. During hypoxia the changes in couplings between HR and RESP time series were not distinctive. However, altered cardiorespiratory interactions were significant during reoxygenation and still ongoing after 30min of recovery. Therefore, findings from JSD2 were confirmed by JSD3. Analyses approved that the JSD2 method is deficient to figure out small changes in short-term cardiovascular time series due to hypoxia. Indeed, using JSD2 decrease and equilibrium changes between two beat-to-beat fluctuations were coded only by one symbol which results in a limited consideration of detailed autonomic regulation. In addition, it can be assumed that small changes which did not arise from autonomic regulation like noise (e.g. generated by sampling) or artifacts can be excluded by applying a threshold for symbol transformation. Introducing an additional symbol for time series transformation an enhanced (high resolution) coupling analyses of autonomic regulation by means of symbolic dynamics is achieved.

Limitations of this study are on the one side the small number of enrolled newborn piglets (N=7). However, in experimental animal studies it is rather usual to investigate only such "small" samples, especially in the case of newborns. On the other side, the huge number of determined JSD-indices in combination with the small sample size might further influence the statistics. Therefore, we performed the Bonferroni-Holm adjustment to minimize the possible statistical error.

V. Conclusion

It might be suggested that the application of JSD3 offers more and detailed information about cardiovascular and cardiorespiratory coupling leading to an increased knowledge about regulatory mechanism of autonomic regulation. The application of this method might be useful for monitoring critical human newborns in case of reduced and recovered oxygen supply.

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References

[1] S. K. Sinha, and S. M. Donn, "Fetal-to-neonatal maladaptation," *Semin Fetal Neonatal Med*, vol. 11, no. 3, pp. 166-73, Jun, 2006.

[2] R. Bauer, "Stupor and coma: pathophysiology of hypoxia--ontogenetic aspects," *Suppl Clin Neurophysiol*, vol. 57, pp. 681-7, 2004.

[3] P. M. Gootman, and N. Gootman, "Postnatal changes in cardiovascular regulation during hypoxia," *Adv Exp Med Biol*, vol. 475, pp. 539-48, 2000.

[4] P. M. Gootman, N. Gootman, and B. J. Buckley, "Maturation of central autonomic control of the circulation," *Fed Proc*, vol. 42, no. 6, pp. 1648-55, Apr, 1983.

[5] M. Baumert, T. Walther, J. Hopfe et al., "Joint symbolic dynamic analysis of beat-to-beat interactions of heart rate and systolic blood pressure in normal pregnancy," *Med Biol Eng Comput*, vol. 40, no. 2, pp. 241-5, Mar, 2002.

[6] A. Voss, S. Schulz, R. Schroeder et al., "Methods derived from nonlinear dynamics for analysing heart rate variability," *Philos Transact A Math Phys Eng Sci*, vol. 367, no. 1887, pp. 277-96, Jan 28, 2009.

[7] U. Zwiener, and R. Bauer, "Marked reduction of brainstem blood flow in artificially ventilated newborn piglets during normoxia and normocapnic hypoxia," *Intensive Care Med*, vol. 29, pp. 2277-2284, 2003.

[8] N. Wessel, A. Voss, H. Mahlberg, C. Ziehmann, H.U. Voss, A. Schirdewan, U. Meyerfeldt, and J. Kurths, "Nonlinear analysis of complex phenomena in cardiological data," Herzschrittmachertherapie und Elektrophysiologie, vol. 11, (no. 3), pp. 159-173, 2000.

[9] C. Hemmelmann, A. Ziegler, V. Guiard et al., "Multiple test procedures using an upper bound of the number of true hypotheses and their use for evaluating high-dimensional EEG data," *J Neurosci Methods*, vol. 170, no. 1, pp. 158-64, May 15, 2008.

[10] A.J. Rohan and S.G. Golombek, "Hypoxia in the term newborn: part three--sepsis and hypotension, neurologic, metabolic and hematologic disorders," *MCN Am J Matern Child Nurs*, vol. 34, (no. 4), pp. 224-33; quiz 234-5, Jul-Aug 2009.