Joint symbolic dynamic analysis of beat-to-beat interactions of heart rate and systolic blood pressure in normal pregnancy

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Abstract—*Pregnancy induces important changes in the autonomic control. Measures of heart rate (HR) variability and systolic blood pressure (SP) variability are sensitive to those changes. The interactions between HR and SP are complex and strongly non-linear. Therefore they cannot be completely described by linear analysis techniques. A study of joint symbolic dynamics is presented as a new short-term non-linear analysis method to investigate the interactions between HR and SP. Continuous, non-invasive 30 min blood pressure recordings (Portapres) of 25 pregnant and 14 non-pregnant women were analysed. Time series of beat-to-beat HR and SP were extracted. Using the concept of joint symbolic dynamics, HR and SP changes were transformed into a bivariate symbol vector. Subsequently, this symbol vector was transformed into a word series (words consisting of three successive symbols), and the probability of occurrence of each word type was calculated and compared between both groups. Significant differences were found in five word types between pregnant and non-pregnant women: $w_{0,4}$(0.021 ± 0.011 against 0.008 ± 0.006; $p = 0.022$), $w_{4,6}$(0.020 ± 0.010 against 0.007 ± 0.003; $p = 0.001$), $w_{3,2}$(0.004 ± 0.003 against 0.007 ± 0.003; $p = 0.038$), $w_{6,5}$(0.009 ± 0.007 against 0.023 ± 0.008; $p < 0.001$) and $w_{3,6}$(0.011 ± 0.007 against 0.023 ± 0.008; $p = 0.001$). Joint symbolic dynamics provides an efficient non-linear representation of HR and SP interactions that offers simple physiological interpretations.*

Keywords—*Heart rate variability, Blood pressure variability, Pregnancy, Portapres, Symbolic dynamics*

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1 Introduction

ASSESSING AUTONOMIC control provides information about patho-physiological imbalances, e.g. preceding sudden cardiac death (LANZA *et al.*, 1998; STEIN and KLEIGER, 1999; STYS and STYS, 1998). Over the last ten years, primarily heart rate variability (HRV) was explored to improve our knowledge about cardiovascular regulation (HUIKURI *et al.*, 1999; TASK FORCE, 1996). Recently, HRV analysis has become widely accepted in medicine, but still little is known about underlying control loops linking the different subsystems. Besides respiration control, blood pressure regulation is a principal task of autonomic co-ordination. Whereas the respiratory system must ensure a sufficient oxygen level, blood pressure maintenance is essential for oxygen and nutrient transportation. Therefore new approaches have concentrated on multi-modal assessment of heart rate (HR), systolic blood pressure (SP) and respiration (RESP).

Using conventional signal-processing techniques, such as cross-correlation and cross-spectral power density analysis, linear dependencies of HR, SP and RESP have been found (AKSELROD *et al.*, 1987; BASELLI *et al.*, 1986). However, owing to non-linear interdependency, non-stationary behaviour and superimposed noise, those techniques are often inadequate for biological data (HOYER *et al.*, 1998*a*; ROSENBLUM *et al.*, 1998).

As the coupling between HR, SP and RESP is assumed to be strongly non-linear, several methods have been developed that consider those non-linear dynamics. Assuming that HR and RESP are two self-sustained oscillators, measures of phase synchronisation and its coupling strength can be derived (CENSI *et al.*, 2000; GONZALEZ *et al.*, 2000; SCHAFER *et al.*, 1998). Phase synchronisation implies some interrelationship between the phases of the oscillators, whereas the amplitudes can be generally uncorrelated. As an adaptation of cross-correlation, mutual information has been introduced to analyse the non-linear dynamics of the cardiorespiratory system (POMPE *et al.*, 1998). Furthermore, estimations of conditional

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entropy, predictability, correlation integral, correlation dimension and maximum correlation have been applied to assess the coupling strength (HOYER *et al.*, 1998*a*; *b*; PALUS and HOYER, 1998; PORTA *et al.*, 1999; 2000; WESSEL *et al.*, 2000). Another approach is based on bispectral analysis techniques (SCHACK *et al.*, 1995). Autoregressive models enable time variate analysis of two signals. Here, non-linear interdependencies are accounted for via bicoherence function analysis (WITTE *et al.*, 2001).

Experimental data from various studies on autonomic co-ordination, in healthy humans, newborns and patients after myocardial infarction, emphasise the importance of multi-modal assessment (CENSI *et al.*, 2000; HOYER *et al.*, 1998*a*; LEDER *et al.*, 2000).

However, in the bivariate HR and SP analysis, a different method has become of major importance. The 'sequence method' (BERTINIERI *et al.*, 1985; MALBERG *et al.*, 1999) seeks for special patterns, such as an increase in systolic blood pressure coupled with a decrease in HR, or *vice versa*. These patterns are associated with the baroreceptor reflex, and its quantitative description is used for assessing the baroreceptor reflex sensitivity.

Pregnancy-induced alterations in autonomic control are well known and, for HRV, already published (VOSS *et al.*, 2000). Knowledge about changes in HR and SP interactions, however, is still limited to one phenomenon, the baroreceptor reflex.

To characterise the beat-to-beat interactions of HR and SP in a more complex way, we introduce a new method, joint symbolic dynamics (JSD). In this way, the study of dynamics simplifies to the description of bivariate symbol sequences. Some detailed information has been lost, but some of the invariant, robust properties of the dynamics have been kept. Especially in HRV analysis, univariate symbolic dynamics has already been successfully applied (VOSS *et al.*, 1994; 1996).

Therefore we hypothesise that JSD provides enhanced information about pregnancy-induced changes in the interactions between HR and SP.

2 Methods

2.1 *Data recording and pre-processing*

We recorded the blood pressure in 25 healthy pregnant women (PRE, week of gestation: 32 ± 6; range: 21st–40th week) and 14 non-pregnant age-matched (28 ± 5 against 28 ± 6 years) controls (NPRE) with the Portapres system*. This monitor achieves continuous non-invasive measurement of blood pressure by applying a servo-controlled finger pressure cuff, based on the 'volume-clamp-method' of PENAZ *et al.* (1976), completed by Wesseling's calibration criteria (WESSELING *et al.*, 1995). The accuracy of this technology has been investigated in various studies (SILKE and MCAULEY, 1998). Although these findings are sometimes contradictory, accepted opinion affirms that a reliable measurement of the blood pressure variability is obtained, but also an individually varying shift in the absolute pressure values (IMHOLZ *et al.*, 1998). Blood pressure was recorded in a supine position during the late morning hours, over a period of 30 min, with a sampling frequency of 200 Hz and a resolution of 1 mmHg.

The time series of HR and SP were extracted using the 'BeatFast' pattern recognition software package†. Ectopic beats and other disturbances were excluded and interpolated by an adaptive variance estimation algorithm, considering the variance within the time series just before and directly after the gap (WESSEL *et al.*, 2000).

2.2 *Joint symbolic dynamics*

If x is the bivariate sample vector of HR and SP (eqn 1), and l^{HR} and l^{SP} are threshold values, then s represents a bivariate symbol vector (eqn 2), gained by transforming x into a symbol alphabet according to eqns 3 and 4.

$$x = \{[x_n^{HR}, x_n^{SP}]^T\}_{n=0,1,\ldots} x \in R \tag{1}$$

$$s = \{[s_n^{HR}, s_n^{SP}]^T\}_{n=0,1,\ldots} s \in 0, 1 \tag{2}$$

$$s_n^{HR} = \begin{matrix} 0 : (x_n^{HR} - x_{n+1}^{HR}) \leq l^{HR} \\ 1 : (x_n^{HR} - x_{n+1}^{HR}) > l^{HR} \end{matrix} \tag{3}$$

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

In the following, the threshold values are set to zero ($l^{HR} = 0$, $l^{SP} = 0$).

Thus, the bivariate symbol vector s consists of $a = 4$ symbols. Further, s is fractionalised to words (bins) w_k of length k (KURTHS *et al.*, 1995). The maximum length of the words is restricted by the probability of occurrence $p(w_k)$ of each word type and therefore, indirectly, by the number of measured samples. With 30 min recording time and a mean heart rate of 75 beats min^{-1}, x contains 2250 samples, and thus s has a length of $N = 2249$. As words with a length greater than three would be statistically insufficiently represented (KURTHS *et al.*, 1995; VOSS *et al.*, 1996), the maximum length of words is limited to $k = 3$ (eqn 5) spanning over an 8×8 vector matrix W, from word type $[000,000]^T$ to $[111,111]^T$ (Fig. 1). To obtain an easier representation, the word types' binary symbol sequences of HR and SP are decimal coded as $w_{HR,SP}$. For example, word type $[001,100]^T$ is equal to $w_{1,4}$ and word type $[010,001]^T$ is equal to $w_{2,1}$.

$$p(w_k) = \frac{N}{a^k} = \frac{2249}{4^3} = 35.14 \tag{5}$$

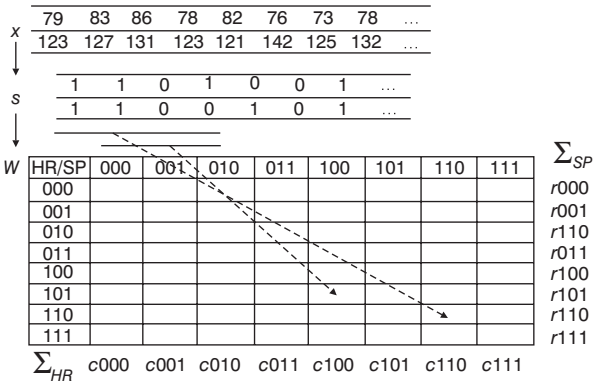

Fig. 1 *Transformation of vector x, which contains bivariate heart rate and systolic blood pressure samples, into symbol vector s and word distribution matrix W. x: beat-to-beat heart rate in beats min^{-1}/beat-to-beat systolic blood pressure in mmHg; s: symbol 1: increasing values/symbol 0: decreasing and equal values; W: row: symbol sequence of heart rate changes; column: symbol sequence of systolic blood pressure changes; r_{HR} = row sum; c_{SP} = column sum*

*Model 2, TNO Biomedical Instrumentation, The Netherlands

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To compare the word type distributions between data sets of different length, the sum of all counted words is normalised to 1. The normalised probabilities of all single word types' occurrences were computed as $p_n(w_{HR,SP})$, the sum of each column was computed as c_{SP}, and the sum of each row was computed as r_{HR} in W (equations (6) and (7)).

$$c_{SP} = \sum_{HR} W_{HR,SP} \tag{6}$$

$$r_{HR} = \sum_{SP} W_{HR,SP} \tag{7}$$

Further, word types were defined as 'dominant' if their probabilities of occurrence $p_n(w_{HR,SP})$ were greater than 0.05 and were defined as 'seldom' if they were less than 0.003.

To compare these parameters between the groups of pregnant and non-pregnant healthy women, we computed simple statistics, including group mean, standard deviation and a two-tailed t-test. The (global) significance level was set at $p_g = 0.05$. Considering the problem of multiple testing, the necessary (local) significance level (p_l) of a single parameter from an observed v-dimensional parameter space must fulfil Bonferroni's inequality (eqn 8) to guarantee (global) significance, as follows:

$$p_l < \frac{p_g}{v} \tag{8}$$

In our case, for $v = 64$ word types and $v = 16$ row and column sums, the local significance levels are $p_l = 0.00078$ and $p_l = 0.0031$.

3 Results

Figs 2 and 3 display the group-averaged three-dimensional plots of the probability distribution density matrix W in NPRE and PRE.

Table 1 contains dominant and seldom occurring word types of group NPRE, including group mean and standard deviation. The word types $w_{4,3}$, $w_{1,6}$ and $w_{0,7}$ are dominant in NPRE, whereas $w_{0,0}$, $w_{6,2}$, $w_{6,4}$, $w_{6,6}$, $w_{0,1}$, $w_{1,1}$, $w_{2,2}$ and $w_{4,4}$ occur seldom. Table 2 shows all dominant and seldom occurring word types in the group of pregnant women. Dominant word types in PRE are $w_{4,3}$, $w_{1,6}$, $w_{0,7}$ and $w_{4,7}$. The word types $w_{6,0}$, $w_{7,2}$, $w_{6,4}$ and $w_{7,6}$ occur seldom in PRE. Word types that differ

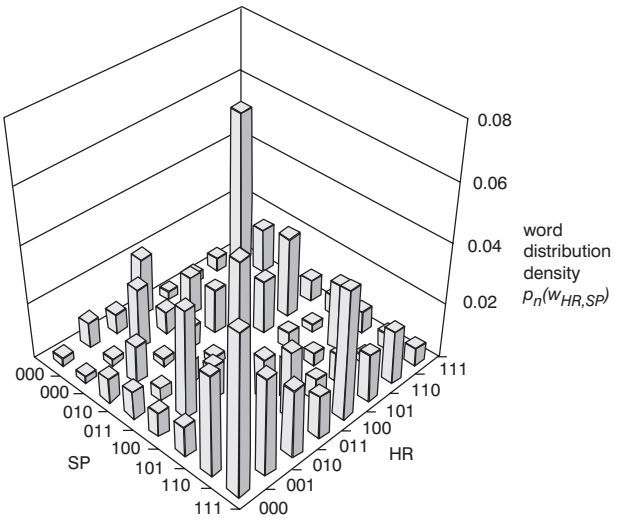

Fig. 2 *Averaged word distribution density in NPRE. HR = behaviour of three successive interbeat intervals. SP = behaviour of three successive systolic blood pressure changes*

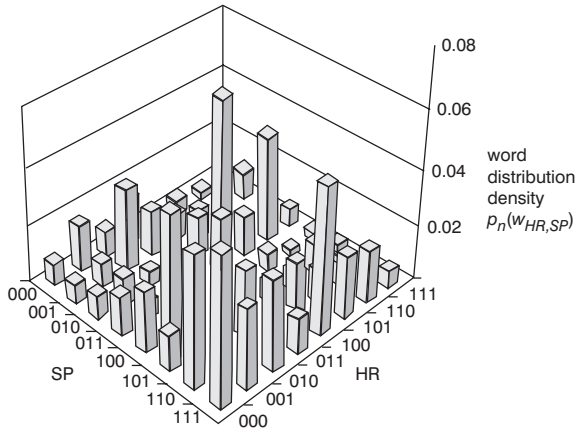

Fig. 3 *Averaged word distribution density in PRE. HR = behaviour of three successive interbeat intervals. SP = behaviour of three successive systolic blood pressure changes*

significantly between both groups are shown in Table 3, including group mean, standard deviation, t-test p-values p_l and corrected global p-values p_g. In PRE, the word types $w_{0,4}$ and $w_{4,6}$ occur significantly more frequently, and the word types $w_{3,2}$, $w_{6,5}$ and $w_{3,6}$ occur less frequently in comparison with NPRE. Table 3 also displays the significant row and column sums. Only r_7 (i.e. r^{111}) differs significantly and is decreased in PRE (0.038 ± 0.02 against 0.067 ± 0.033, $p_g = 0.025$).

Table 1 Normalised probabilities of dominant ($p_n > 0.05$) and seldom occurring word types ($p_n < 0.003$) in word distribution matrix of NPRE

Word type	Abbreviation	Mean	SD
dominant			
$[100,011]^T$	$w_{4,3}$	0.078	0.021
$[001,110]^T$	$w_{1,6}$	0.063	0.017
$[000,111]^T$	$w_{0,7}$	0.054	0.029
seldom			
$[000,001]^T$	$w_{0,1}$	0.002	0.002
$[001,001]^T$	$w_{1,1}$	0.002	0.002
$[010,010]^T$	$w_{2,2}$	0.002	0.002
$[100,100]^T$	$w_{4,4}$	0.002	0.001
$[000,000]^T$	$w_{0,0}$	0.003	0.002
$[110,010]^T$	$w_{6,2}$	0.003	0.002
$[110,100]^T$	$w_{6,4}$	0.003	0.002
$[110,110]^T$	$w_{6,6}$	0.003	0.001

Mean = group mean; SD = standard deviation

Table 2 Normalised probabilities of dominant ($p_n > 0.05$) and seldom occurring word types ($p_n < 0.003$) in word distribution matrix of PRE

Word type	Abbreviation	Mean	SD
dominant			
$[100,011]^T$	$w_{4,3}$	0.061	0.033
$[000,111]^T$	$w_{0,7}$	0.053	0.025
$[001,110]^T$	$w_{1,6}$	0.052	0.026
$[100,111]^T$	$w_{4,7}$	0.052	0.019
seldom			
$[110,000]^T$	$w_{6,0}$	0.002	0.002
$[111,010]^T$	$w_{7,2}$	0.002	0.002
$[110,100]^T$	$w_{6,4}$	0.002	0.001
$[111,110]^T$	$w_{7,6}$	0.002	0.002

Mean = group mean; SD = standard deviation

Table 3 Significantly different word probabilities and row sum probability between PRE and NPRE

		PRE		NPRE		*t*-test	
Word type	Abbreviation	mean	SD	mean	SD	p_l	p_g
$[000,100]^T$	$w_{0,4}$	0.021	0.011	0.008	0.006	0.00035	0.0224
$[100,110]^T$	$w_{4,6}$	0.020	0.010	0.007	0.003	0.00002	0.0011
$[011,010]^T$	$w_{3,2}$	0.004	0.003	0.007	0.003	0.00060	0.0384
$[110,101]^T$	$w_{6,5}$	0.009	0.007	0.023	0.008	0.00001	0.0006
$[011,110]^T$	$w_{3,6}$	0.011	0.007	0.023	0.008	0.00002	0.0011
r_{HR} 111	r_{HR7}	0.038	0.020	0.067	0.033	0.00158	0.0253

Mean = group mean; SD = standard deviation; p_l = local p-value; p_g = global p-value

4 Discussion

In this paper, we introduced a novel approach for the investigation of HR and SP interactions based on JSD. Transforming HR and SP times series into a bivariate symbol vector reveals significant differences in the interactions of both signals between pregnant and non-pregnant women. This is confirmed by earlier findings showing that pregnancy has an impact on autonomic control (VOSS *et al.*, 2000).

The word distribution matrix W enables a coarse-grained quantitative assessment of short-term beat-to-beat HR and SP interactions. The word distribution within W clearly shows the presence of deterministic structures, because stochastically independent HR and SP patterns would result in a more or less equal distribution. Supporting this assumption, the three most dominant words, $w_{4,3} = [100,011]^T$, $w_{1,6} = [001,110]^T$ and $w_{0,7} = [000,111]^T$, are the same in both groups. Moreover, all these words display an opposite behaviour (if SP decreases, HR increases, and *vice versa*) that could be associated partly with the baroreceptor reflex as the most important short-term blood pressure regulator.

It should be noted that the 'sequence method' (BERTINIERI *et al.*, 1985) considers only monotonous patterns for assessing the baroreceptor reflex, i.e. word type $w_{0,7} = [000,111]^T$. Although it is known that pregnancy decreases the baroreceptor reflex sensitivity (VOSS *et al.*, 2000), the word type $w_{0,7}$ does not significantly differ between PRE and NPRE. An explanation for this could be that the 'sequence method' assesses the slope of baroreceptor reflex activation, whereas JSD takes activation frequency and duration into account.

One of the seldom occurring words ($w_{6,4} = [110,100]^T$) is the same in both groups (seldom means $p_n(w_{HR,SP}) < 0.003$). However, in group NPRE, there are twice as many seldom occurring word types as in group PRE. This indicates a lower variation in the interactions of HR and SP in NPRE and could express an adapted regulation in pregnancy. Five of all the seldom occurring word types are symmetric ($w_{0,0} = [000,000]^T$, $w_{6,6} = [110,110]^T$, $w_{1,1} = [001,001]^T$, $w_{2,2} = [010,010]^T$ and $w_{4,4} = [100,100]^T$) and are only seldom occurring in NPRE. Assuming that symmetric word types partly reflect suppressed baroreceptor reflex activity, the increased occurrence of these word types in PRE probably indicates a reduced baroreceptor reflex activity in pregnancy. Significant differences between both groups occur in five word types. Two of them ($w_{3,2} = [011,010]^T$, $w_{6,5} = [110,101]^T$) contain '010' and '101' patterns in systolic blood pressure and probably indicate pulsus alternans effects (SURAWICZ and FISCH, 1992).

Considering the row and column sum probabilities, the sequences included in r_7 appear significantly more frequently in NPRE than in PRE. Surprisingly, this is not related to any specific word type in that row, and thus it might not be directly associated with HR and SP interactions. By focusing on significant words, further studies must refine these patterns and their physiological meaning.

Although heart rate and blood pressure variability parameters did not show considerable differences depending on the age of gestation (VOSS *et al.*, 2000), this has to be proved for the JSD in further studies.

As the introduced approach quantifies the non-linear interactions between HR and SP within intervals of four heart beats, we mainly consider para-sympathetically mediated components (HF) of autonomic regulation rather than sympathetically mediated components (LF) under these current specifications (AKSELROD *et al.*, 1987). Longer intervals presuppose an exponentially growing recording time. Words exceeding four beats require a measurement time of at least 2 h and are not applicable in most cases, even when non-invasive monitoring techniques are used.

Besides the 'sequence method' as an established method for non-invasive baroreceptor reflex sensitivity estimation, HR and SP interrelationships are often analysed via cross-spectral coherence function techniques (BASELLI *et al.*, 1986), particularly in the LF band (COOLEY *et al.*, 1998). However, the coherence function normally provides no, or only part, information about interactions between both time series. Linear correlation and mutual information measure the linear and non-linear similarities of signals but, as with the coherence function, they provide insufficient information about interactions between the time series. Measures of complexity and coupling strength (HOYER *et al.*, 1998*a*; *b*; PALUS and HOYER, 1998; PENAZ *et al.*, 1976; POMPE *et al.*, 1998; PORTA *et al.*, 1999; 2000; ROSENBLUM *et al.*, 1998; SCHAFER *et al.*, 1998) are mostly applied to characterise the coupling between heart rate and respiration. Only a few authors (CENSI *et al.*, 2000; PORTA *et al.*, 2000) investigated coupling or co-ordination between heart rate and blood pressure. In contrast to those techniques, JSD considers and classifies different patterns of short-term interactions between heart rate and blood pressure and offers enhanced and detailed information about linear and non-linear interrelationships.

In conclusion, JSD provides a new representation of HR and SP short-term interactions and the opportunity for an easy physiological interpretation. JSD shows significant pregnancy-dependent alterations in the autonomic regulation. Therefore this method could also be suitable for the investigation of gestation-related disorders, such as pre-eclampsia.

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