Joint Order Pattern Analysis to Assess Baroreflex Coupling of SBP and PI Series in Rats

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Abstract

The baroreceptor reflex (BRR) bears the important part in short term blood pressure (BP) control. Joint order pattern analysis is proposed to assess the complex nature of BP and pulse interval (PI) dynamic. The BP and PI signals were acquired from conscious radiotelemetred Wistar male rats with intact BRR loop and pharmacologically opened BRR loop at different levels *using blockade of* β-adrenergic, α-adrenergic and M-cholinergic receptors. The study revealed increase in complexity of relationship between BP and PI due to opening of BRR loop, as measured by permutation entropy and probability density function of transcriptions translating BP variations into PI responses. Synchronization measure significantly decreases in open BRR loop changing from 0.22 towards the values characteristic for random and independent data (0.02). It follows that BRR buffers random BP and PI changes and increases their synchronization.

1. Introduction

Insight in complex heart rate (HR) and blood pressure (BP) interactions reveals the important aspects of baroreceptor reflex (BRR) control of short-term BP fluctuations. The BRR works as a negative feedback system that produces unidirectional changes of BP and heart period. As it plays the central role in regulation of the cardiovascular system, the prognostic value of a baroreflex alterations have been studied in various pathological situations [1-3]

In order to identify the presence and characteristics of the interactions between HR and BP, the BRR loop was pharmalogically opened in conscious rats at different levels using drugs. The BBR loop was disrupted by blocking the effect of neurotransmitters released from the efferent fibers of the parasympathetic (vagus) nerve or sympathehic nerves of BRR on their postsynaptic receptors.

The complexity and synchronization measure between systolic blood pressure (SBP) and pulse interval (PI) series was assessed using their symbolic representation. Permutation entropy [4], the complexity measure defined for a single time series, was independently calculated for both of the cardiovascular variables. Based on the same symbolic representation, the information measures are used to quantify the degree of synchronization between SBP, as the source series and PI as the target series, using methodology presented in [5]. The timing aspect of interactions between SBP and PI was assessed using probability density function (pdf) of transcriptions which map SBP changes into PI responses. The deviation of transcription pdf from uniform pdf was measured by Kullback-Leibler divergence.

The changes of the measures of complexity and synchronization in open BRR loop reveal the importance of BRR regulation in the short-term arterial blood pressure buffering and heart rate control. The calculated measures may serve as fast and robust tool offering the insight into BRR functioning even from short and noisy clinical data.

2. Materials and methods

2.1. Experimental protocol

Animals: experiment were done in conscious male Wistar out bred rats (320-350g) under standard laboratory conditions with water and food ad libitum.

Surgery: rats were submitted to surgical procedure during which implants TA11 PA-C40 (Transoma Medical, DSI Inc., USA) were inserted in aorta. After full recovery period (10 days), rats were re-operated for quick insertion of catheter in jugular vein for drug injections. Two days later rats were submitted to four different protocols.

Protocol 1_CNTRL was designed as a control group in which saline (0.9% NaCI) was injected to n=9 rats (1 ml/kg i.v. followed 0.5 ml/kg/h i.v. infusion).Protocol 2-PRA was designed to investigate the contribution of the vascular part of the sympathetic nervous system, under selective blockade of α_1 adrenergic receptors in blood

vessel wall by prazosin in n=6 conscious rats (1 mg/kg i.v. bolus continued by 0.5 mg/kg/h infusion). Protocol 3-METO was designed to investigate the contribution of' the part of the sympathetic nervous system directed to the heart, under selective blockade of β adrenergic receptors by metoprolol (2 mg/kg i.v. bolus continued by 1 mg/kg/h infusion) in n=6 conscious rats. In protocol 4-ATRO we investigated the contribution of the parasympathetic part of autonomic nervous system by blocking the muscarinic receptors in the heart by atropine methyl bromide (1 mg/kg i.v. bolus, followed by 0.5 mg/kg/h i.v infusion) in n=3 conscious rats.

2.2. Signal preprocessing

Continuous recording of blood pressure pulse wave was done using DSI radio telemetry system. Pulse pressure, sampled at 1000 Hz, was used for extraction of SBP by identification of the maxima in the pulse wave signal. The distance between the SBP maxima was used as an estimation of pulse interval durations. Recorded time series of PI and SBP consisted of up to 13 five-minute recordings made with two-minute brakes. From each time-series, 1024 consecutive samples were chosen, the same ones for both PI and SBP series. The frequently employed stationarity test was done [6]. The remaining stationary study sample included 50 series for protocol 1-CNTRL, 68 series for protocol 2-PRA, 43 ones for protocol 3- METO and 28 ones for protocol 4-ATRO. In order to filter out respiration induced fluctuations, SBP and PI beat to beat series were low-pass filtered by a moving average on 10 cardiac cycles [7,8].

2.3. Permutation entropy

For the time series $\{x_n\}_{n=1,2...N}$, lets denote by $s=(x_0,x_1,...,x_{k-1})$ the sequence of the length k extracted from x. The association of the sequence s to its symbolic representation S is done using rank-ordered indices of the sequence components. The sequence s=(134, 138, 135 139), for example, would be presented with the symbol S=(0,2,1,3). This symbolization method proposed in [4] does not consider the occurrences of equal values, since small random perturbation can always be added to avoid these cases. The symbolization of the sequences of the length k produces k! permutations π of order k. For each permutation π relative frequency can be determined as:

$$p(\pi) = \frac{\#\{n \mid n \le N - k + 1, (x_n, x_{n+1}, \ldots x_{n+k-1}) \text{is type } \pi\}}{N - k + 1} \quad (1)$$

In the case of infinite time series, $p(\pi)$ can be exactly determined as $N \to \infty$, yet this limit exist if the time series fulfills weak stationarity condition. The permutation entropy (PE) of order k is defined as:

$$H(k) = -\sum p(\pi) \log p(\pi) \quad (2)$$

where the sum includes all k! permutations of order k. PE is the information contained in comparing k consecutive values of time series [4]. Naturally, $0 \le H(k) \le \log(k!)$ holds, where the lower bounds reveal ordered series with increasing or decreasing values, while completely random series exhibit uniform distribution of permutation probabilities and therefore maximal PE. The study done in [4] has showed that entropies, up to order 6, can be reliably estimated already from N=1000 values.

PE was separately determined for SBP series and for PI series in different experimental protocols.

2.4. Joint order pattern analysis

If the presented symbolization procedure is applied on SBP and PI series, two symbolic series s_{PI} and s_{SBP} are obtained. Governed by the principles of BRR functioning, the extent to which the changes in the SBP series, the source series, induce the unidirectional changes in PI, the target series, has to be determined.

For any two symbols S_1 and S_2, there exist a symbol T, referred to as transcription, such that the composition $T[S_1]=S_2$. The exact action of transcription is defined as follows [5]: if the $S_1=(i_0,i_1,...i_{k-1})$ and $T=(j_0,j_1,...j_{k-1})$, then: $T[S_1] = (i_{j_0}, i_{j_1}, ..., i_{j_{k-1}})$.

The set of all possible k! symbols S_i can be partitioned into sets of order classes C^J. The transcription T has the order J, i.e. $T \in C^J$, if $T^J=I$, where I=(0,1,2,..k-1) is the identity transcription. The complexity of the transcription T is assessed by a dissimilarity measure between the source and the target symbol, given by the minimum number J of recursive applications of transcription T to yield the identity symbol I [5]. Figure 1 shows the symbolization procedure for k=4 and transcription symbols translating SBP series into the target, PI series.

For k=4, there are order-1 to order-4 classes (C^1,C^2,C^3,C^4) present. The transcription matrix for k=4 has $(4!)^2$ elements.

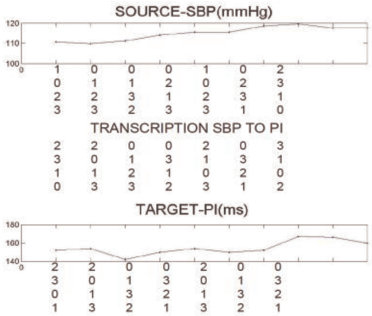


Figure 1. The symbolization procedure for k=4, SBP, source symbols on the top, PI, target symbols on the bottom and transcriptions that map SBP into PI symbols.

The probability density function (pdf) of transcriptions $P_T(k)$ can be obtained for each of the possible *l=1...k!* transcriptions as:

$$P_{T_l}(k) = \sum_{\Omega=\{(i,j)|T_l[S_i]=S_j\}} P(S_i, S_j) \quad (3)$$

where $P(S_i,S_j)$ is the joint probability density of symbolic representations out of which the marginal probability densities of symbols $P(s_{SBP})$ and $P(s_{PI})$ can be calculated.

Pdf of transcriptions $P_T(k)$ was compared with pdf $P_T^{surr}(k)$ of transcriptions obtained using sets of mutually independent isodistributional surrogate data. Isodistributional (ID) surrogates are obtained by randomly shuffling the samples of original time series, preserving the length, mean, standard deviation and histogram of the original time series, but being otherwise uncoupled. Different permutations were used for SBP and PI series. For each set of original data 39 surrogates were generated and $P_T^{surr}(k)$ averaged. However, the results have shown that the pdf in ID surrogate data, i.e. mutually independent data streams, is uniform.

The information measure which can be used to asses the deviation of $P_T(k)$ from $P_T^{surr}(k)$, i.e. uniform distribution, is Kullback-Leibler divergence:

$$E_{KL}(P, P^{surr}) = \sum_l P_{T_l}(k) \log_2 \left(P_{T_l}(k) \Big/ P_{T_l}^{surr}(k)\right) \quad (4)$$

Since E_{KL} is not symmetric measure, the symmetric form is derived using harmonic mean of $E_{KL}(P,P_{surr})$ and $E_{KL}(P_{surr},P)$

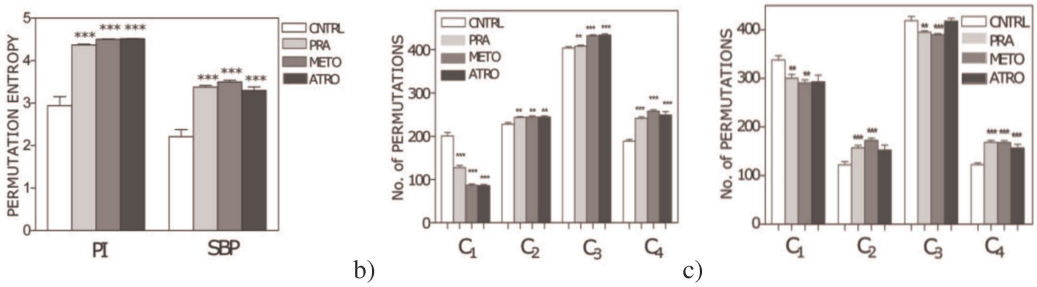
$$S_{KL}(k) = \frac{E_{KL}(P, P^{surr}) \cdot E_{KL}(P^{surr}, P)}{E_{KL}(P, P^{surr}) + E_{KL}(P^{surr}, P)} \quad (5)$$

E_{KL} can be calculated summing over all of the transcriptions or only over the transcription belonging to certain class J, when the resulting S_{KL} measure is denoted S^J_{KL}.

3. Results

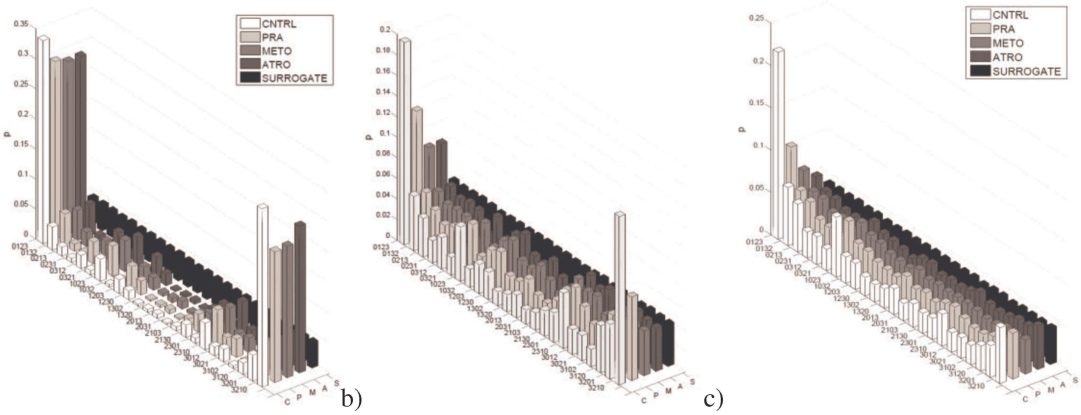
Permutation entropy (PE) was done separately in PI and SBP series under different experimental protocols. The significant increase of PE after opening of the BRR loop indicates the increase in complexity of both of the time series. The further insight is given by exploring the number of permutations of different order in PI and SBP separately (Figure 2b and 2c, respectively). The complexity increase can be explained by the significant decrease in C^1 permutations, followed by significant increase in the number of permutations of higher order. SBP series performs differently only when C^3 permutations are in question as their number decreases in protocols PRA and METO where sympathetic influences to the blood vessels and the heart, respectively, are cut.

The joint order pattern analysis revealed that dominant patterns in symbolic representations of SBP series - $P(s_{SBP})$ are still increasing and decreasing patterns (Figure 3a). On the other hand, the pattern of changes in PI series - $P(s_{PI})$ significantly differs from CNTRL protocol in open BRR loop tending to uniform pdf characteristic to ID surrogate data (Figure 3b).



a) b) c)

Figure 2. a) PE for PI and SBP separately; b) No. of permutations of different order for PI in experimental protocols; c) No. of permutations of different order for SBP. Significance is given in comparison with CNTRL protocol using one-way ANOVA (*, p<0.05, ** p<0.01; *** p<0.001)



a) b) c)

Figure 3. Marginal pdf of symbolic representations for SBP (panel a) and PI (panel b) and transcription pdf (panel c)

The pdf functions of transcriptions that map the changes of SBP into PI responses (Figure 3c) reflects the decrease in the relative frequency of identity transcription T=I, which marks the identical pattern of changes in two time series. The transcription pdf is given as well in Fig. 4. representing the relative frequencies of permutation classes. The shape of pdf functions indicate that the dominance of the C^3 permutations is characteristic for random data, this dominance is perturbed in CNTRL protocol by significant presence of C^1 permutations, under completely functional BRR. The opening of the BRR is dominantly characterized by the decrease in relative frequency of C^1 permutations and increase in relative frequency of C^3 and C^4 permutations.

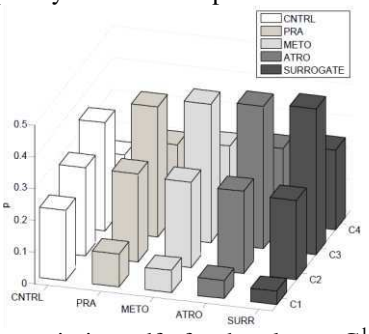


Figure 4. Transcription pdf of order classes C^1, C^2, C^3 and C^4 for all experimental protocols

The synchronization measure S_{KL} calculated from transcription pdf (Fig. 5) recognizes the weak lag synchronization of SBP and PI series. S_{KL} measure reaches maxima for the delay of 4 heart beats between the SBP and PI series. In protocol PRA the S_{KL} measure significantly drops, while for the protocols ATRO and METO, with cutting of the autonomic influences directed to the heart, S_{KL} reflect almost complete loss of synchronization.

The S_{KL} measure calculated for each order class separately behave in the similar manner as global S_{KL} measure. It has been noted that in protocol ATRO, when the contribution of parasympathetic part was blocked, the synchronization measure, although small, has repeatedly reached the maximum for the lags of 1 and 2 heart beats. This maximum is indicating by the box in Fig.5.

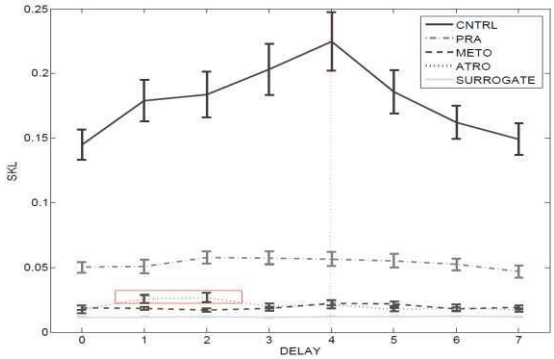


Figure 5. The changes of S_{KL} measure for the delays between SBP and PI ranging from 0 to 7 heart beats.

4. Conclusions

Results confirm the contribution of the autonomic nervous system to the complexity and synchronisation of SBP PI shot-term dynamics. PE reveals the lack of BRR responses and increase of more complex symbolic patterns due to opening of the BRR loop. These results are concordant with the joint order pattern analysis where the presence of higher order transcriptions in opened BRR loop indicates the change in relationship of SBP and PI series. Simpler synchronization state, such as under the fully functional BRR reflex, is characterized by the dominance of low order classes. The maximum of S_{KL} measure indicates that for the time series of rats the time delay between the SBP changes and corresponding PI responses should be set to 4 heart beats, as previously proposed by Oosting et al. [7].. Pdf of transcriptions reveals the complexity of relationship between SBP and PI series and reflects the transcription effort. Further studies in humans are warranted to validate the diagnostic and the prognostic potential of the methods.

References

[1] Ormezzano O, Cracowski JL, Quesada JL, Pierre H, Mallion JM, Baguet JP. Evaluation of the prognostic value of baroreflex sensitivity in hypertensive patients: the EVABAR study. J Hypertens 2008;26;1373-1378.

[2] Narkiewicz K, Grassi G. Impaired baroreflex sensitivity as a potential marker of cardiovascular risk in hypertension. J Hypertens 2008;26;1303-1304.

[3] Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. AmJ Physiol Regul Inter Comp Physiol 2002;283;R815-R826.

[4] Bandt C, Berndt P. Permutation entropy: natural complexity measure for time series. Phys Rev Lett 2002;88(17);174102

[5] Monetti R, Bunk W, Aschenbrenner T. Characterizing synchronization in time series using information measures extracted from symbolic representations. Phys Rev E;79; 046207

[6] Bendat, Piersol. Random data analysis and measurment procedures, New York, Willey Interscience, 1986.

[7] Oosting J, Struijker-Boudier HAJ, Janssen BJA. Validation of a continuous baroreceptor reflex sensitivity index calculated from spontaneous fluctuations of blood. J Hypertens 1997; 15(4): 391-9

[8] Waki H, Kasparov S, Katahira K, Shimizu T, Murphy D, and Paton JF Dynamic exercise attenuates spontaneous baroreceptor reflex sensitivity in conscious rats. Exp Physiol 2003; 88: 517–526

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