

Response to Active Standing of Heart Beat Interval, Systolic Blood Volume and Systolic Blood Pressure: Recurrence Plot Analysis

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Abstract Recurrence quantitative analysis (RQA) indexes of beat-to-beat heart-beat interval and systolic blood pressure (SBP) have helped to understand the dynamical response to active standing. The peripheral blood volume is another variable of the cardiovascular control system with a crucial role during active standing since re-distribution of blood volume is necessary to counteract the gravity force and to provide enough blood supply to vital organs. Beat-to-beat photoplethysmographic systolic blood volume (SBV) oscillations may be useful to study the cardiovascular control if it is considered as a regulatory system with relevant local differences compared to blood pressure regulation. There are no previous reports of the SBV dynamical response to active standing. In this work we study simultaneously the dynamical response of heart-beat interval, SBP and SBV to active standing through comparison of RQA indexes evaluated during supine position and during active standing in 19 healthy volunteers. We show that in response to orthostatic stress, SBV oscillations have dynamic changes similar, but not identical, to SBP and the heart-beat interval. This suggests that these three variables are complementary for a better evaluation of the cardiovascular dynamics.

1 Introduction

The heart-beat varies after every single cycle (heartbeat, i.e. beat-to-beat), in order to adjust itself to the continuously changing living conditions that an organism must face. Although the heart possesses its own intrinsic cardiac nervous system with

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thousands of neurons of diverse type, it has to coordinate with and integrate to the information coming from the entire body [1]. We know that this is done mainly by the autonomous nervous system (ANS) via its two subdivisions: sympathetic and parasympathetic, each of them with complementary and apparently reciprocal functions and their characteristic medium lag activation and fast inhibition. However the two branches of the ANS are not algebraically additive. Instead they interact in a dynamic fashion and either reciprocity or co-activation of both branches may occur [2]. Besides all this, there are upper coordination centers at the central nervous system, and our bodies count on long term regulatory processes like endocrine or paracrine systems; short term mechano-sensorial signals to communicate the degree of effort or total mechanical work done and demanded; and metabolic sensors that detect oxygen, glucose or ATP availability in every single cardiac cycle [2–4].

Given all the afore mentioned factors participating in heart rate regulation, it is useful to count with a well-described autonomic stress paradigm as is the change from the supine to the standing position (orthostatism), which is associated to a reduction in vagal outflow to the sinus node and with an increase in sympathetic nerves activity to compensate the sudden drop of blood pressure to the brain; the fast pressure drop produced by the blood sequestered in the limbs can be compared with a traumatic loss reducing the cardiac filling pressure [5]. Vasoconstriction reflex and increased heart rate are very important adjustments to the orthostatic stress; it has been assumed that the level of sympathetic vasomotor activity elicited in response to orthostatic stress reflects the degree of unloading of the arterial and cardiopulmonary baroreceptors. These adjustments must remain as long as the standing up position persists [5–7].

Linear heart rate variability analysis used to evaluate autonomic regulation during orthostatism is characterized by increased mean heart rate, decreased variability and mean total power in the frequencies spectrum [8]. More recently several non-linear indexes have been evaluated in healthy subjects and in patients with different pathologies [9–11]. Besides describing nonlinear properties of the heart rate variability, clinical applications have been shown for some of them (e.g. independent prognosis of cardiac death in survivors of myocardial infarction) [8, 11]. However, rigorous application of most nonlinear time series analysis methods need long and stationary time series and their uncritical application to biological data can lead to serious misleading conclusions [12, 13]. Therefore, nonlinear methods with applicability to short and noisy data, as in the case of heart rate variability, are continuously developed with the aim of revealing non evident changes in the cardiovascular control system [14, 15]. This is the case of Recurrence Plots Analysis. Recurrence is a basic feature of many dynamical systems, including physiological ones, and it measures the repeated occurrence of a given state of the system through a quantitative recurrence analysis (RQA). The application of RQA has shown that several properties of heart rate recurrence plots are different in diabetic patients compared to healthy subjects [16], and also that several RQA indexes are sensitive to orthostatic challenge in healthy and neuropathy subjects, helping to understand the mechanism that regulate the chronotropic activity of the heart [17–20]. However, heart rate variability by itself is not enough to understand the cardiovascular regulation [21].

1.1 Systolic Blood Pressure and Systolic Blood Volume

The importance of the sympathetic nervous system in the short-term regulation of blood pressure via the modulation of peripheral vascular tone and cardiac output is well established [7]. The study of the systolic blood pressure (SBP) variability is used to assess the autonomic sympathetic regulation towards the blood vessels, and combined with heart rate it is used to evaluate the baroreflex mechanism, mainly by estimation of the baroreflex sensitivity [22]. The dynamical behavior of SBP has also been studied with nonlinear methods, including the recurrence plots analysis [23]. From the cardiovascular point of view, blood pressure is one of the main variables that the cardiovascular system is trying to keep bounded within a dynamic range that guarantees enough perfusion to all body tissues. In this sense, blood pressure can be considered as a regulated variable, while heart rate is one of the effectors that is permanently adjusted by the control system [24]. The dynamical behavior of these two variables is strongly associated by feedback loops of the cardiovascular system, for example, the negative feedback loop between blood pressure and heart rate in the baroreflex mechanism [25]. Given this association, heart rate and SBP variability are not orthogonal variables, and therefore the understanding of the cardiovascular regulation with only these two variables remains limited [26].

As a third study variable, in this work we consider the blood volume variability, evaluated by the photoplethysmographic systolic blood volume (SBV) [5, 26]. SBV is also a variable of the control system and may add relevant information regarding the cardiovascular regulation. SBV is modulated by direct influence from the sympathetic nervous system but not by the parasympathetic nervous system [7, 25–27], and other mechanisms involved, such as the baroreflex, are also relevant [26, 27]. SBV behavior has been characterized mainly by linear methods such as spectral analysis [25, 28]. However, little is known about the dynamical properties of SBV, and there are no previous studies of the recurrence plot of this variable. Considering their intricate physiological association, it is important to learn how these three physiological variables co-evolve: SBP, SBV and heart-beat interval in different physiological context; and as a first approximation we are using the recurrence plots and QRA to compare their dynamical changes during the orthostatic challenge in healthy patients.

The aim of this study was to assess the effects of active orthostatic stress as revealed by recurrence plots and RQA indexes for three relevant cardiovascular physiological outputs: heart beat interval, SBP and for the first time, SBV oscillations.

2 Methods

Nineteen healthy volunteers, age 20–40 years old were included in the study. The volunteers fulfilled the following inclusion criteria: no known history of diabetes mellitus, cardiovascular disease or any other kind of chronic or acute disease, no medication indicated, no-smokers. All subjects were asked to avoid intake of stim-

ulants such as caffeine during 12h before the study and they gave their informed consent to participate in this study. The study protocol is in accordance with the principles outlined in the Declaration of Helsinki of 1975 (as revised in 1989), and it was approved by the Ethics Committee of the hospital (Instituto Nacional de Cardiología Ignacio Chávez, México), protocol number 12–763.

Non-invasive blood pressure recordings were obtained with a Finometer and blood volume was estimated with a photoplethysmograph during supine position and orthostatism at a sampling frequency of 200 samples per second. The pressure sensor was secured on the middle finger of the left hand, with the arm resting on a sling to reduce hand movements. A calibration was made for each person by compressive sphygmomanometry. In each body position, the recording started after 5 min of stabilization and lasted 15 min. The recordings were processed to identify SBP and SBV value of each heartbeat, and to calculate all inter beat intervals (IBI). The pertinence of using only systolic values was shown before by our group [26].

2.1 Beat Detection Process

Ad-hoc techniques were implemented by computer programs in Matlab (Mathworks, Inc) described previously [26]. Briefly, the blood pressure signal was filtered by a second derivative algorithm, it was rectified to positive values and a threshold was applied in order to find the peaks that correspond to SBP [29]. Correct identification of SBP for all heartbeats was verified manually. IBI was obtained from the time difference of SBP between consecutive heartbeats.

2.2 Systolic Blood Volume

The photoplethysmographic oscillations are associated with blood volume changes in the microvascular bed of tissue that are observed around the average blood volume [5, 26]. Since PPG pulse is not a direct quantitative measurement it is represented in arbitrary units (a.u). We used a two LED reflectance system that has been characterized previously [30].

2.3 Recurrence Plot Construction

Recurrence plots exhibit characteristic large and small scale patterns that are caused by fundamental dynamic behavior, e.g. short diagonal lines reveal similar local evolution of different parts of the trajectory, while horizontal and vertical black lines appear when a state does not change for some time. Random processes do not exhibit

those linear structures [31, 32]. The main step for the visualization of recurrence in a time series or data set is the calculation of the $N \times N$ matrix,

$$R_{i,j} = \Theta (\varepsilon_i - \|\vec{x}_i - \vec{x}_j\|),$$

where N is the number of data, ε_i is a predefined threshold distance, $\|\cdot\|$ is a norm (e.g. the Euclidean norm), and Θ is the Heaviside function. A multidimensional state space is reconstructed from the one dimensional beat to beat time series, applying a time delay embedding method. Each point in the reconstructed phase space represents the state of the system at a given moment and is determined by m coordinates of a given embedding dimension. To obtain all these reconstructed data we used the tools developed by Norbert Marwan and colleagues, the Cross Recurrence Plot Toolbox for Matlab [available from the toolbox for complex systems (TOCSY) webpage: <http://tocsy.pik-potsdam.de/crp.php>].

Embedding delay was estimated with both autocorrelation function and mutual information minima without finding significant differences. Embedding dimension was estimated by means of false nearest neighbor method. Since the estimated dimension was smaller than 10 in all times series, we set the embedding dimension = 10, which is in accordance with the recommendation of Webber [33] and other references [34, 35]. The distances between individual points in the matrix corresponding to a state of the system at a given time were calculated using the option Maximum norm fixed recurrence rate (“rr”) in the toolbox for auto recurrent plots [15, 31, 36].

Besides the visual inspection of recurrence plot that help to recognize different characteristics between different physiological conditions, we applied a quantitative analysis of the generated patterns (RQA). We measured the following parameters: percentage of determinism (the percentage of recurrence points forming diagonals from all recurrence points), mean diagonal length, Lmax (length of the longest diagonal line), trapping time (time in which the dynamics remains trapped in a certain state), mean length of the vertical lines, laminarity (proportion of recurrence points forming vertical or horizontal lines), Vmax (maximal verticality), T1 (recurrence time of first type) and T2 (recurrence times of second type) [31]. Specifically, T2 is able to detect very weak transitions with high accuracy, both in clean and noisy environments. T1 has the distinguished merit of being more robust to the noise level and not sensitive to the parameter changes of the algorithm [37]. Also entropy was obtained. It is defined as the Shannon information entropy of the line length distribution [38]. Shannon Entropy is related to the amount of data needed to identify a particular state of the system.

Normal distribution of RQA indexes was tested with Kolmogorov-Smirnov tests. The variables that did not satisfy the normality test were transformed by a natural logarithm. Mean values of the RQA indexes were compared between supine position and active standing with paired t tests. A p value <0.05 was considered statistically significant (ANOVA). The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program, version. 15.0(SPSS, Inc).

3 Results

3.1 Recurrence Plots

Figures 1 and 2 show two examples of the three underlying time series used to produce each RP of healthy volunteers in clinostatism and orthostatism: IBI, SBP and SBV. Globally they show a significant content of high frequency oscillations (“fast cycles”), combined with some oscillations of lower frequencies. In the corresponding recurrence plot during supine position, the high frequency oscillations are reflected in regularly distributed diagonal lines, parallel to the identity line. The small diagonals are trapped in well-formed squares and rectangles. The white vertical spaces correspond to slow transient changes; and it is also possible to recognize a slow drift along some time series. Some differences were found in the associated patterns to IBI, SBP and SBV in the same person. In most cases the SBP and SBV plots seem like filters of the pattern observed in the IBI plot, with less fast cycles (Figs. 1 and 2 in supine position), like a progressive smoothing effect.

In contrast, in the standing up position there is an increase in both intercalated white regions and the density of points forming square zones (laminarity). Compared to supine position, during orthostatism the time series shows a decrease in the high frequency oscillations and increase in low frequency oscillations (Figs. 1 and 2).

The corresponding recurrence plot has important qualitative changes: it still shows diagonal lines but they are less fine and more scattered than the ones observed in supine position, while more regions have white vertical spaces in correspondence with slow transient changes in the time series. With careful inspection or visual training it could be possible to know if the plots correspond to a standing up person.

3.2 Recurrence Indexes from QRA

Table 1 summarizes our findings. In response to active standing there was no change in embedding dimension of all variables, but the embedding delay of both IBI and SBV increased significantly. On IBI, active standing caused significant increment in laminarity, trapping time, recurrence time of the first type (T1) and recurrence time of the second type (T2). In SBP, the only significant changes in response to active standing were: decrease in mean diagonal length, longest diagonal length, and increase in T1. In response to active standing, SBV showed significant increase in laminarity, T1 and T2.

3.3 In Trend and Out of Trend

Looking at Table 1 it is possible to appreciate that there were three indexes with p-values that almost reached statistical significance ($0.05 < p < 0.10$). We decided to examine the individual variation of those groups of indexes: the group with sig-

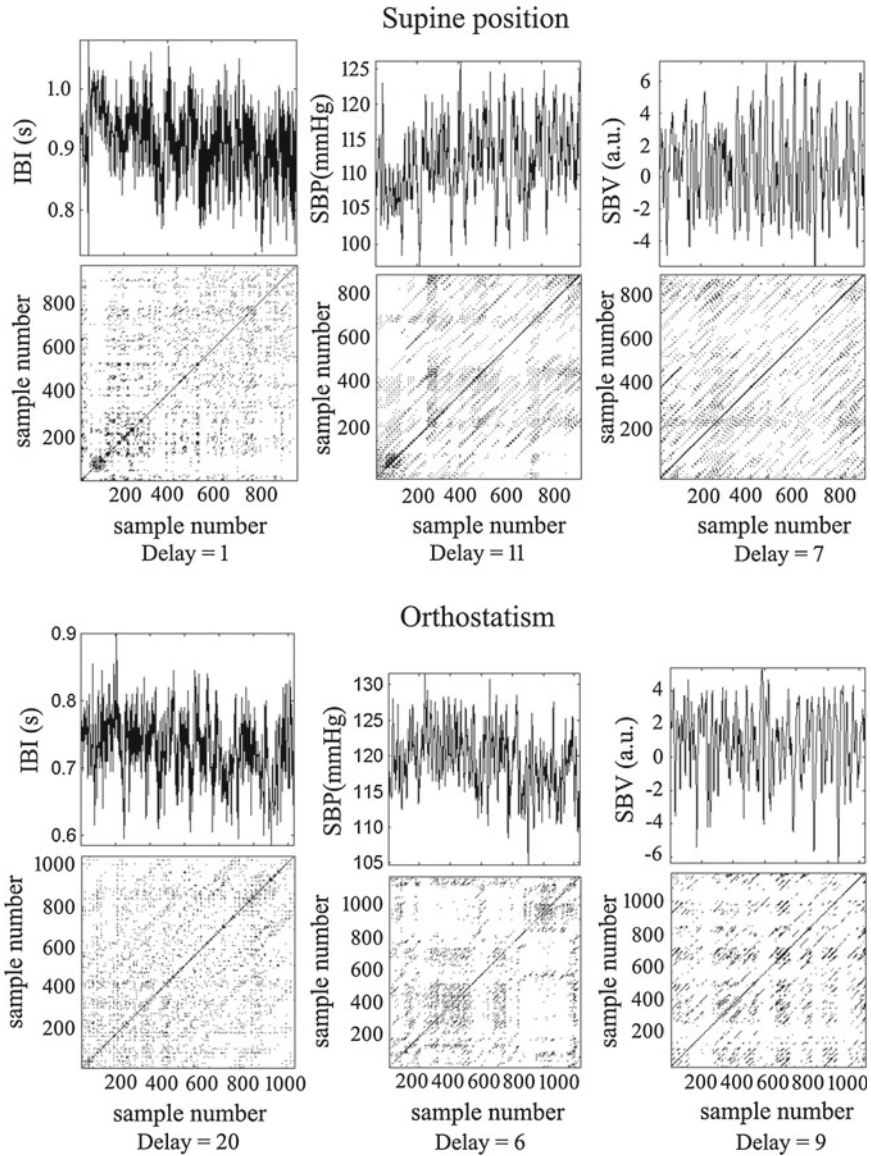


Fig. 1 Time series and recurrence plots from subject number 13. IBI= inter beat interval, SBP = systolic blood pressure, SBV= systolic blood volume. Recurrence plots parameters were: embedding dimension = 10, fixed recurrence rate = 7%, and ad-hoc embedding delay (estimated with each corresponding auto-correlation function)

nificant differences and the group with differences almost statistically significant. Figure 3 shows examples of the first group of indexes.

We found, for example, that laminarity variation for IBI increased in response to orthostatism in 18 out of 19 subjects, although in a different extent within subjects

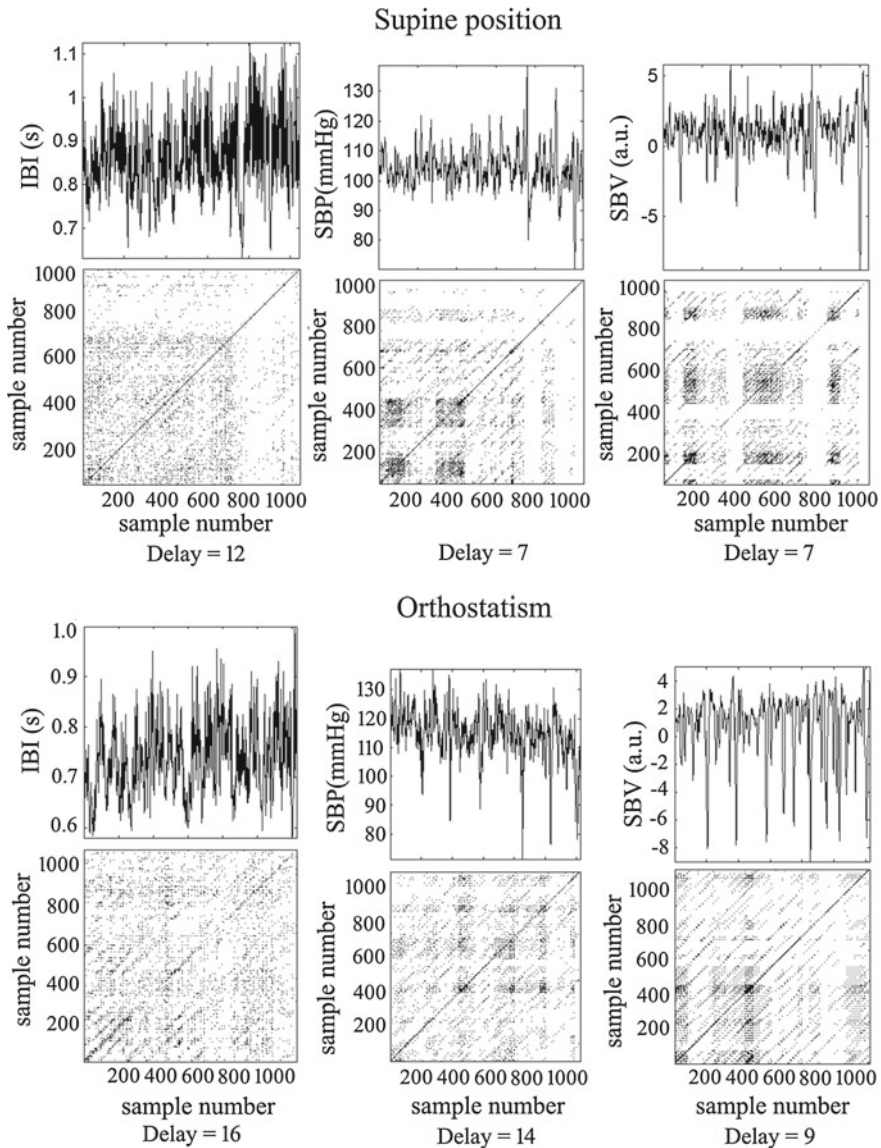


Fig. 2 Time series and recurrence plots from subject number 8. IBI = interbeat interval, SBP = systolic blood pressure, SBV = systolic blood volume oscillations. Recurrence plots parameters were: embedding dimension = 10, fixed recurrence rate = 7%, and ad-hoc embedding delay (estimated with each corresponding auto-correlation function)

(Fig. 3a). The same expected consistency was found in IBI recurrence rate which decreased during orthostatism (Fig. 3b), and in TT1 of SBP and laminarity of SBV which increased during orthostatism (Fig. 3c, d). These types of consistent responses to orthostatism was observed for all other indexes with significant p-values ($p < 0.05$).

Table 1 Quantitative recurrence analysis of heart beat intervalvariability (IBI), systolic blood pressure (SBP) and systolic blood volume oscillations (SBV), evaluated from 19 healthy subjects during resting conditions (supine position) and during active standing (orthostatism)

	IBI	SBP	SBV
<i>Supine position</i>			
Embedding delay (heartbeats)	7 ± 5*	9 ± 3	8 ± 2*
Embedding dimension	6 ± 1**	6 ± 1	6 ± 1
Recurrence rate (%)	6.3 ± 0.4*	5.9 ± 0.4	6.4 ± 0.3**
Ln (determinism)	-0.78 ± 0.45	-0.40 ± 0.32	-0.29 ± 0.23
Mean diagonal length	3.24 ± 1.67	3.72 ± 1.41*	4.23 ± 1.83
Ln (longest diagonal length)	3.14 ± 0.96	4.04 ± 0.92*	4.13 ± 0.85*
Ln (entropy)	-0.06 ± 0.56	0.27 ± 0.45**	0.38 ± 0.45
Laminarity	0.48 ± 0.12*	0.70 ± 0.13	0.79 ± 0.11*
Trapping time	2.60 ± 0.32*	3.37 ± 0.82	37.2 ± 28.4
Maximal verticality	22.4 ± 12.7	33.0 ± 19.0	37.2 ± 28.4
Recurrence type of 1st type	12.0 ± 1.6*	11.5 ± 3.2*	11.7 ± 2.5*
Recurrence type of 2nd type	17.3 ± 2.6*	23.9 ± 7.5	31.1 ± 10.5*
<i>Orthostatism</i>			
Embedding delay (heartbeats)	14 ± 5	9 ± 4	9 ± 2
Embedding dimension	7 ± 1	6 ± 1	5 ± 1
Recurrence rate (%)	5.6 ± 0.6	6.0 ± 0.3	6.2 ± 0.2
Ln (determinism)	-0.66 ± 0.22	-0.53 ± 0.19	-0.22 ± 0.11
Mean diagonal length	2.58 ± 0.20	2.68 ± 0.36	3.72 ± 1.00
Mean diagonal length	2.58 ± 0.20	2.68 ± 0.36	3.72 ± 1.00
Ln (longest diagonal length)	2.76 ± 0.80	2.91 ± 0.77	3.62 ± 0.76
Ln (entropy)	-0.02 ± 0.20	0.04 ± 0.23	0.46 ± 0.20
Laminarity	0.67 ± 0.09	0.72 ± 0.09	0.88 ± 0.06
Trapping time	3.05 ± 0.30	3.13 ± 0.51	4.59 ± 1.23
Maximal verticality	27.8 ± 14.2	25.9 ± 15.2	48.2 ± 29.7
Recurrence type of 1st type	15.2 ± 2.9	13.7 ± 2.3	13.1 ± 2.8
Recurrence type of 2nd type	28.4 ± 6.2	28.2 ± 8.4	45.8 ± 18.9

* p ≤ 0.05 (supine position versus orthostatism, paired t-test)

** 0.05 < p < 0.10 (supine position versus orthostatism, paired)

On the other side, when we review the indexes with almost significantly differences like Shannon’s Entropy of IBI, or determinism of SBP, we identify two or three well defined subsets of response to orthostatism within each index (Fig. 4a, b). This implies that there can be two or three types of variations in the response to orthostatism, even though they all correspond to young healthy subjects. Due to the high dispersion in the response of each index, the t-test between supine position and orthostatism did not reach a significant difference.

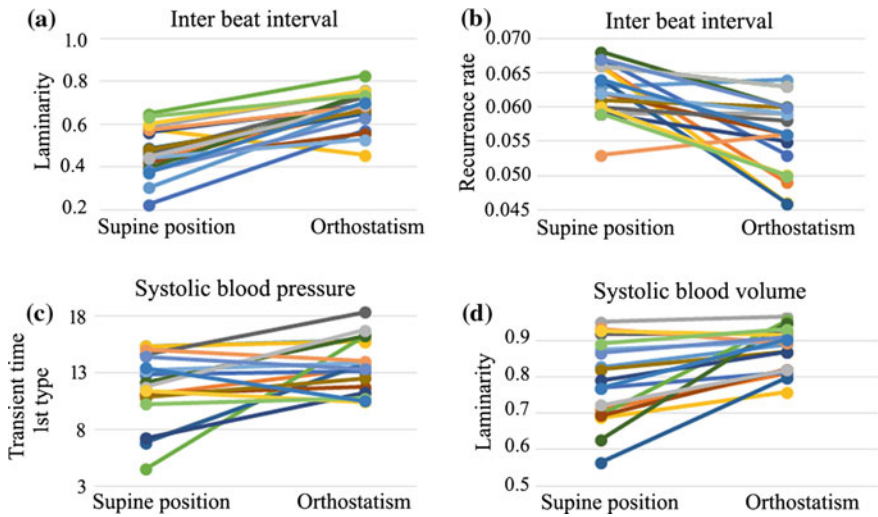


Fig. 3 Examples of quantitative recurrence plot analysis indexes with a consistent response to orthostatism (showed as a significant paired t-test, $p < 0.05$, between supine position and orthostatism)

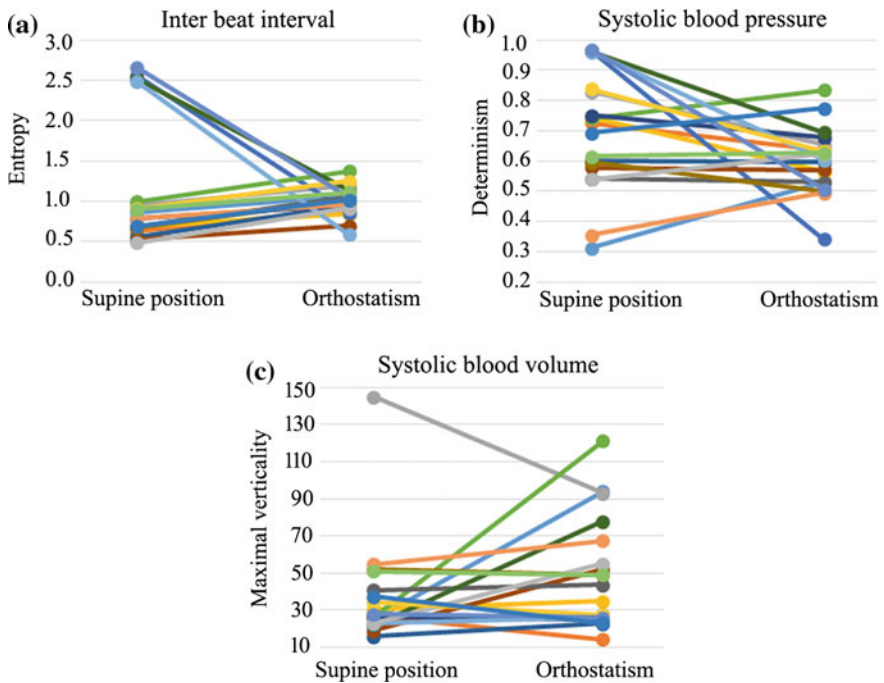


Fig. 4 Examples of quantitative recurrence plot analysis indexes with no significant changes in response to orthostatism (showed as paired t-test, $0.05 < p < 0.10$, between supine position and orthostatism)

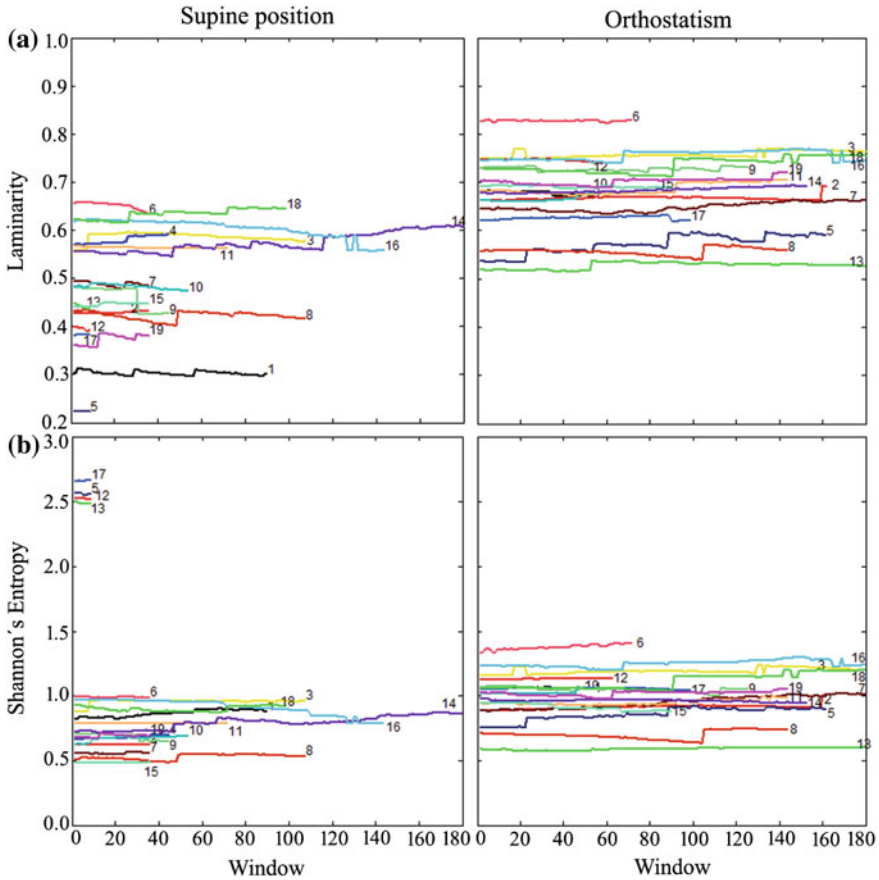


Fig. 5 Temporal variation in inter beat interval QRA indexes: **a** example of a QRA index with statistically significant difference ($p < 0.05$) between supine and orthostatism, **b** example of a QRS index with non-significant difference ($0.05 > p > 0.10$)

Another way to consider this inter-individual variation in indexes which were almost statistically different is to analyze the temporal evolution of relevant indexes in both studied conditions. Figure 5 (upper left panel) shows the temporary evolution of IBI Laminarity for the supine condition and Fig. 5 (upper right panel) for the orthostatic position.

Most of the subjects have the same type of change in their QRA index, independently of their particular trajectory, and only a few deviate from the overall trend. On the other hand, for the QRA indexes that resulted almost significant, such as the Shannon's Entropy (Fig. 5, lower panels) we found cases that markedly deviate from the overall trend. However, these cases correspond to healthy persons too.

4 Discussion

In our study the recurrence plots showed a consistent pattern of more clustering of points during orthostatism with respect to supine position. The quantitative assessment with the RQA indexes confirmed these observations of the effect of orthostatic stress in healthy subjects: IBI, SBP and SBV variability and complexity were reduced and the characteristics of their dynamics were changed by orthostatism, which is consistent with previous reports about RQA from IBI alone [19, 20], or from IBI and SBP [23].

In standing position, that represents a physiologically activated state, theRP had higher laminarity and trapping time, that is, a long permanence of the system in a particular state, with a reduction in the number of states that are visited, as can be seen for a larger proportion of white spaces. It seems that for a more activated condition (i.e. active orthostatism) the predominance of a smaller number of dynamic states is important, and therefore, the demanded physiological status is reached with a smaller set of combined adjustments.

There were similarities in the response of SBV and IBI, but the response of RQA indexes was not identical in the 3 evaluated variables. There was more parallelism in the significant QRA indexes between IBI and SBV than between IBI and SBP. This suggests that despite the known high correlation between these 3 variables, the cardiovascular control exerts different influences on them in response to active standing. Previous work with different methodology showed that during passive orthostatism, complexity of IBI decreases while complexity of SBP remained unchanged, suggesting that complexity indexes from IBI and SBP provide complimentary information [21]. Our work agrees with these ideas considering the following: (i) we observed a response to active orthostatism that is consistent with decreased complexity in several recurrence plot indexes of IBI, SBP and SBV, (ii) there were fewer indexes in SBP that changed significantly, compared to IBI, indicating that SBP have less dynamical changes in response to active standing, and (iii) several of the indexes that changed significantly in SBP were different from those that changed in IBI or SBV, which also supports the hypothesis that these 3 variables provide complementary information.

Our results also indicate an association between changes in dynamical behavior of IBI, SBP and SBV with an increased sympathetic predominance. This confirms that the autonomic modulation of the cardiovascular control responds to the orthostatic stimulus [20], but also suggests that some other mechanism, as regional vasomotor activity may have an important role. The finding can be suitable to appreciate a differential condition of the three variables in a clinical evaluation of health and disease.

Clinical considerations of decreased variability, complexity and IBI nonlinear dynamics reflected in RQA indexes has been used for detection of heart rate deregulation in various pathological conditions including chronic fatigue syndrome, hypertension, diabetes mellitus, chronic renal failure, and ventricular arrhythmia [19, 20]. One of the greatest interests of clinicians is to be able to associate the condition of

the autonomic balance, or autonomic tone, with the risk of disease or to gain some insights for therapeutics management. For example, in myocardial infarction survivors, the observation of high laminarity has been associated with an increased risk for life threatening arrhythmia [15].

Overactivity of the sympathetic nervous system is both a major early prognostic indicator for hypertension and a conspirator affecting the heart, vasculature, renin-angiotensin system and immune system. As sympathetic overactivity appears to be present before the hypertensive phenotype, its early antagonism should be considered a potential preventative measure before end organ damage becomes irreversible and hypertension becomes drug resistant [39, 40]. Therefore, having new tools to evaluate augmented sympathetic activity in health condition as those here analyzed becomes very relevant.

Another interesting aspect was to review some particular QRA indexes close to reach statistical significance; we applied to them the same methodology and data protocol; so they pose the question of considering a broader spectrum of results as corresponding to a healthy condition. Maybe it is necessary to develop a more personalized approach to distinguish between health and disease or to learn to recognize the individualized evolution to disease. As Richard Levins remarks:

If we fail to define the problem big enough, then many important impacts on a variable come from outside the domain of the problem and are treated as “random” or “error. Contrary to common sense, big problems are often more soluble than small ones [41]

In conclusion, we have shown that in response to orthostatic stress, SBV oscillations have dynamic changes similar but not identical to SBP and IBI. This suggests that these three variables are complementary for a better evaluation of cardiovascular dynamics.

Also we discussed the convenience to develop a more personalized assessment of the physiological condition, for example the level of activity of the sympathetic nervous system based on more statistical indexes and their variances.

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