Analysis of extrema of heartbeat time series in exercise test

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Abstract

The heartbeat time series of the electrocardiogram recorded during exercise test clearly reflects the physiological control mechanism of the autonomic nervous system on heart rate. This series shows both decreasing and increasing trends and variability of the variance. We analyze the series of intervals between two consecutive extrema, i.e. the durations of accelerations or decelerations of heart rate. We compute the distribution of the length of these intervals and their mean in a model of stationary independent variables, where they are independent on the variables distribution. We use the mean length as discriminant statistics to compare stress and recovery phases. Data analysis performed over the heartbeat series of 14 healthy subjects shows significant difference between stress and recovery.

Keywords: Exercise test, extrema, heartbeat, time series, RR interval.
Mathematics Subject Classification 2000: 62P10, 92C55

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1 Introduction

The heartbeat time series is defined as the sequence of time intervals between consecutive R peaks (RR intervals) in an electrocardiogram (ECG). This series reflects the physiological control mechanisms of the heart rate. The main mechanism is the autonomous nervous system, which controls heart rate via the sympathetic and parasympathetic terminations. The variability of the RR sequence, known as Heart Rate Variability (HRV), is used to extract informations on the autonomic system (see [12] and references therein).

One of the situations in which the neuroautonomic control is more evident is during the cardiac exercise test. This test is performed to evaluate the presence of myocardial ischemia. In normal subjects during effort myocardial blood flow increases three or four times compared to rest, as a consequence of increased oxygen request. In ischemic patients coronary artery stenosis does not allow the blood flow increase during effort. Reduced myocardial oxygen supply induces ischemia and consequent modifications in electrophysiological, mechanical and perfusional myocardial faculties. Electrocardiogram, echostress or scintigraphy are respectively employed to detect these modifications.

We consider the routine ambulatory bicycle exercise test of normal subjects monitored by ECG. It is commonly believed that during stress, in which heart rate is increasing, the heart is prevalently under influence of the sympathetic branch and during recovery, in which heart rate is decreasing, the heart is prevalently under influence of the parasympathetic branch.

Spectral analysis [10] is the main tool used to investigate the control of the autonomic system of the heart rate. It is believed that the parasympathetic control is related to high frequency (HR) spectral components of RR sequence (0.15 Hz - 0.4 Hz) and the sympathetic one is related to low frequency (LF) components (0.04 Hz - 0.15 Hz). These results are supported by experiments in humans performed with pharmacological blockade or stimulation such as the tilt test (for example [4]). In 24 hours normal heartbeat there is evidence of a significant difference between positive and negative accelerations [5], suggesting that sympathetic and parasympathetic controls are not symmetric.

In the above situations the RR time series can be supposed to be stationary. In the case of the exercise test the RR series is not stationary showing an evident typical trend (fig.1). In addition the series is heteroschedastic,

i.e. its variability depends on time. This feature was already observed in atrial fibrillation and was proposed to discriminate this pathology [13]. This data can be transformed into a stationary sequence, using a model based on linear dependence of standard deviation versus mean [3]. Atrial fibrillation data are less complex than normal ones, and in particular exercise test data are strongly non stationary, so the above methods do not apply.

Empirical Mode Decomposition (EMD)[9] is a powerful technique for the analysis of non stationary signals. This technique, which was originally formulated for continuous time signals, has been applied also to discrete time series such as the RR sequences [1, 6]. This method is based on the analysis of extrema (local maxima and minima) of the series. The expected number of extrema per unit time has been used as a discriminating statistic in testing non linearity [7]. Mathematical properties of the extrema of the intrinsic mode functions of EMD for continuous signals are non trivial; in the case of white noise some results have been obtained by using numerical simulation [14].

For discrete signals, if the time series is modeled as a sequence of continuous random variables (r.v.), the properties of the extrema are not yet known. The first aim of the present paper is to investigate these properties. From a data series we extract the series defined by the length of monotonicity intervals, i.e. the distance between two consecutive extrema. If the data series is an independent identically distributed (i.i.d.) sequence of continuous r. v., the length of monotonicity interval series is stationary, but nothing is known about its dependence structure; numerical simulation suggests that this sequence is weakly correlated. Hence the univariate discrete density plays a central role in its description. We compute this density, which has the remarkable property of being independent on the distribution of the variables in the data series; we show that the mean is equal to 3/2.

The second aim of the paper concerns the applications of the above ideas to exercise test RR data series. In performing data analysis we have found that the length of monotonicity intervals series extracted from the data series is very close to being stationary and uncorrelated. This series describes the durations of acceleration and deceleration of the heart rate. As above the univariate discrete density of this series plays a central role in its description. We have estimated this density from the data and used the mean as a discriminant statistics. The mean has the following properties:
(i) it is significantly different for increasing and decreasing intervals;
(ii) it is significantly higher than 3/2 both in stress and in recovery phase.

Property (i) reflects the time irreversibility of the RR series, as was already found for other type of data [5, 6]. This also suggests that during exercise the control of the sympathetic and parasympathetic branch of the neuroautonomic system could be quantified by the durations of acceleration and deceleration. Property (ii) can be understood in the light of the result on i.i.d series, for which the value 3/2 is the universal mean of the length of monotonicity intervals. We conjecture that the RR series has a mean higher than 3/2, due to the action of the neuroautonomic system, which prolongates the durations of acceleration and deceleration.

The analysis of extrema is related to the first Intrinsic Mode Function of the EMD, since it concerns only the smallest scale of the series. However the present paper shows that it can be useful for clinical applications and that it is possible to get mathematical results.

We introduce the analysis of extrema and prove some results in the next section. We report on the results of data analysis in the third section; in the fourth section we compare with other methods, in particular with spectral analysis.

2 The analysis of extrema

We model the observed time series $x_1, ..., x_n$ as the realization of a sequence of r. v. $X_1, ..., X_n$, with joint continuous distribution P. We consider the subsets of R^3 : $A = \{x_1 < x_2,\ x_2 > x_3\}$ corresponding to maximum condition and $B = \{x_1 > x_2,\ x_2 < x_3\}$ corresponding to minimum condition. For the sequence $X_i' = (X_i, X_{i+1}, X_{i+2})$, we define the r.v. T_i^{max} and T_i^{min} respectively as the occurrence times of the event A and B.

The analysis of extrema consists in the extraction of two sequences from the original time series. The first one is the monotonicity intervals length, defined as follows. Let us suppose that the first extremum is a minimum, i.e. $T_1^{min} < T_1^{max}$; then we have that $T_i^{min} < T_i^{max}$, for each i. Since the other case can be treated in a similar way, we adopt this assumption in all this section. We define

$$H_i^+ = T_i^{max} - T_i^{min}, \quad H_i^- = T_{i+1}^{min} - T_i^{max}$$

which are the maximal lengths of intervals in which the series is respectively increasing and decreasing. The second sequence is the monotonic

variations, defined as

$$Y_i^+ = X_{T_i^{max}} - X_{T_i^{min}}, \qquad Y_i^- = X_{T_{i+1}^{min}} - X_{T_i^{max}}$$

Thus from the original time series one can extract two sequences

$$H_1^+, H_1^-, H_2^+, H_2^-, \ldots \quad Y_1^+, Y_1^-, Y_2^+, Y_2^-, \ldots$$

By definition the H_i's are positive integer valued r.v. related to the time variable of the original series and the Y_i's are continuous r.v. alternating in sign, related to the values of the series. A more complete description can be given considering the variables $H_0^- = T_1^{min}$, i.e. the length of the interval from 1 to the first minimum and $Y_0^- = X_{T_1^{min}} - X_1$. The sequences H_i's and Y_i's contain information on the shortest time scale of the original series and are reminiscent of the first intrinsic mode function of EMD.

In this paper we focus on the properties of the H_i's under the assumption that the variables X_i are i.i.d. with continuous distribution.
We base our computations on the following classical result [11], which is independent on the distribution of the X_i's

$$P(X_1 < X_2 < \ldots < X_s) = \frac{1}{s!}, \quad s \geq 2 \tag{2.1}$$

and a similar one for the reversed inequality.
We first compute the conditional mean of the H_i's :

$$E(H_1^+ \mid X_1' \in A \cup B) = E(H_1^- \mid X_1' \in A \cup B) = \frac{3}{2} \tag{2.2}$$

The sequence $H_1^+, H_1^-, H_2^+, H_2^-, \ldots$ is defined as the recurrence times of the event $A \cup B$ for the stationary sequence X_i'. The H_i's form a stationary sequence under the conditional probability $P(\quad \mid X_1' \in A \cup B)$ ([2],sec. 6.9) and

$$E(H_1^+ \mid X_1' \in A \cup B) = E(H_1^- \mid X_1' \in A \cup B) = \frac{1}{P(X_1' \in A \cup B)} \tag{2.3}$$

We have taking complements

$$P(X_1' \in A) = P(X_1 < X_2, \quad X_2 > X_3) = P(X_1 < X_2) - P(X_1 < X_2 < X_3)$$

and so

$$P(X_1' \in A) = \frac{1}{2!} - \frac{1}{3!} = \frac{1}{3} \tag{2.4}$$

and since A and B are disjoint and $P(X_1' \in A) = P(X_1' \in B)$ eq. (2.2) follows. A similar argument for the recurrence times L_i^{max}, L_i^{min} gives

$$E(L_1^{max} \mid X_1' \in A) = \frac{1}{P(X_1' \in A)} = 3 \ , \quad E(L_1^{min} \mid X_1' \in B) = \frac{1}{P(X_1' \in B)} = 3 \tag{2.5}$$

We compute the conditional distribution of H_1^+, which despite its simplicity seems to be new.

Proposition For the i.i.d. sequence $X_1, X_2, ...$ if the X_i's have continuous distribution, the variable "length of the monotonicity interval" has a discrete density

$$P(H_1^+ = s \mid X_1' \in B) = 3\left[\frac{1}{(s+1)!} - 2\frac{1}{(s+2)!} + \frac{1}{(s+3)!}\right], \quad s \geq 1 \tag{2.6}$$

Proof We have for $s \geq 3$

$$P(H_1^+ = s-2 \mid X_1' \in B) = P(X_2 < ... < X_s, \quad X_s > X_{s+1} \mid X_1 > X_2, \quad X_2 < X_3)$$

We consider the intersection

$$J = \{X_2 < ... < X_s, \quad X_s > X_{s+1}\} \cap \{X_1 > X_2, \quad X_2 < X_3\}$$

corresponding to "2 is a minimum, the sequence is increasing in 2,..., s , s is a maximum". Hence

$$P(H_1^+ = s-2 \mid X_1' \in B) \ = \ P(J)/P(X_1' \in B), \quad s \geq 3$$

Taking complements we have

$$P(J) = P(X_1 > X_2, \quad X_2 < ... < X_s, \quad X_s > X_{s+1}) =$$

$$P(X_2 < ... < X_s, \quad X_s > X_{s+1}) - P(X_1 < X_2 < ... < X_s, \quad X_s > X_{s+1})$$

and again taking complements for each summand

$$P(J) = P(X_2 < ... < X_s) - P(X_2 < ... < X_s < X_{s+1}) -$$

$$[P(X_1 < X_2 < ... < X_s) - P(X_1 < X_2 < ... < X_s < X_{s+1})]$$

Using eq. (2.1), we get

$$P(J) = \frac{1}{(s-1)!} - 2\frac{1}{s!} + \frac{1}{(s+1)!}$$

and this gives the result. □

One can check the equation

$$\sum_{s=1}^{+\infty} 3 \left[\frac{1}{(s-1)!} - 2\frac{1}{s!} + \frac{1}{(s+1)!} \right] = 1$$

using that the series can be decomposed in the sum of two telescopic series. With similar methods one can also prove that

$$\sum_{s=1}^{+\infty} 3 \left[\frac{1}{(s-1)!} - 2\frac{1}{s!} + \frac{1}{(s+1)!} \right] s = \frac{3}{2}$$

i.e. as expected

$$E(H_1^+ \mid X_1' \in B) = \frac{3}{2}, \quad E(H_1^- \mid X_1' \in A) = \frac{3}{2} \tag{2.7}$$

3 Data analysis

The subjects of our analysis were selected from a group of 28 referred for symptoms and signs suggestive of myocardial ischemia to ECG Laboratory. They underwent the clinical examinations, exercise test, standard 12-leads ECG and scintigraphy. Multistage Bruce protocol diagnosis of inducible ischemia was used according to the current guideline [8]. From the subjects who underwent the test, 14 of them resulted healthy, and are the object of the present study; no other selection criteria has been adopted.

ECG was recorded with the PC-ECG 1200 (Norav Medical Ltd.), which provides output digital signal with an amplitude resolution of 2.441 microV and 500 Hz sampling frequency. The data analysis was performed using the statistical software R [15]. The 50 Hz power-line interference and voluntary muscular activity were removed by using a discrete wavelet transform filter. An automated method was used for R peaks detection from the V5 lead.

The plot of the RR sequence in a typical case is in fig.1. This time series has been smoothed using a moving window average filter with span of 50 beats. The filtered series shows a unique global point of minimum (acme). The original series restricted to beat numbers smaller than acme is called ‘stress phase’; the original series restricted to beat number greater than acme is called ‘recovery phase’.

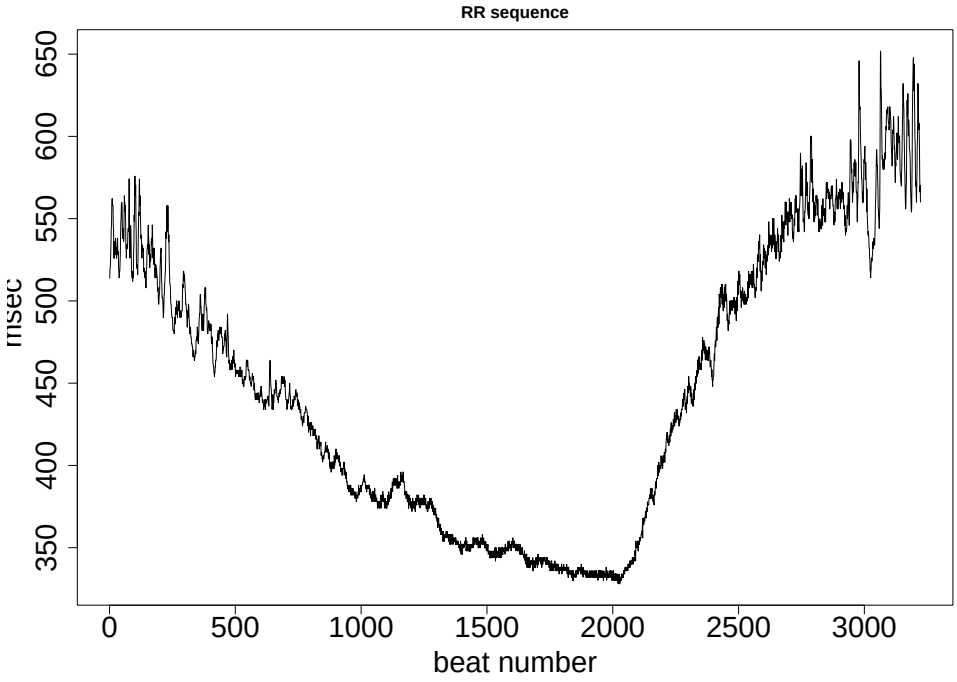

Figure 1: Sequence of RR intervals (in msec) of the exercise test of a normal subject versus the beat number.

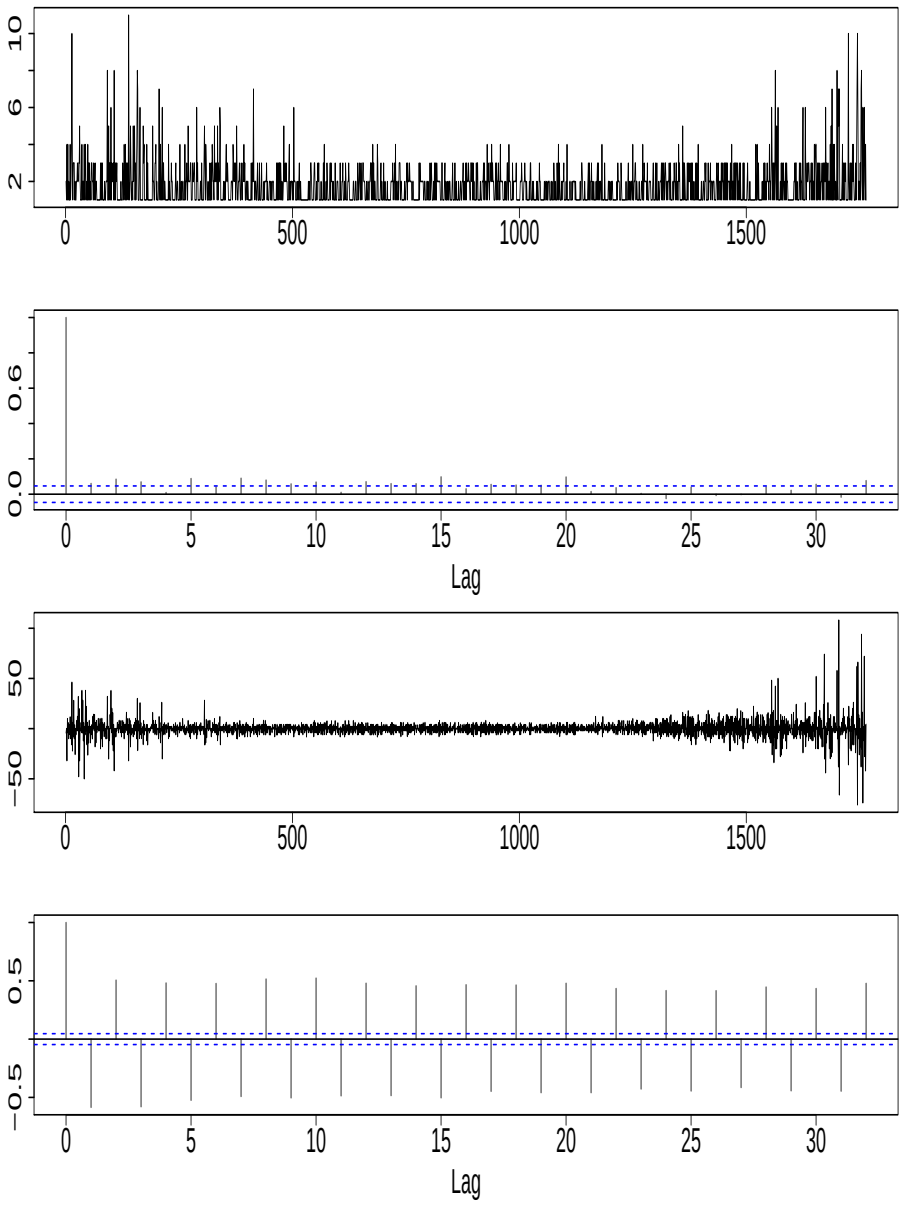

Figure 2: First panel: length of the monotonicity intervals versus the interval number; second: the autocorrelation of above sequence; third: the monotonic variation (in msec) versus the interval number; fourth: the autocorrelation of the above.

Stress and recovery phases are characterized by respectively a decreasing and increasing trend. The trend is not symmetric with respect to acme: this is because the stress phase is driven while the recovery is not. In addition the RR sequence is heteroschedastic: its variability is greater at the start and at the end of the test than near acme.
We extract the two sequences as required by the analysis of extrema: the length of monotonicity interval and the monotonic variation. Both of these reflect the non stationary behavior of the RR series, but in a very different way. The first one, which is shown in the first panel of fig.2, shows a moderate non stationarity behavior with greater values at start and at end of the test. Its autocorrelation function (second panel) is almost everywhere close to the 0.95 significance threshold of an i.i.d. sequence. The monotonic variation, which is alternate in sign, and is shown in third panel, shows a stronger non stationary behavior and its autocorrelation (fourth panel) is above the threshold. This behavior is common to all the cases of our study. Although the autocorrelation functions cannot capture the fine statistical properties of these two series, their comparison suggests that the sequence of monotonicity interval length has weaker correlations. This series is not stationary because even and odd elements are lengths of intervals in which the series is, say, increasing and decreasing. If the positive and negative accelerations of heart rate are under control of the two different branches of the neuroautonomic system, we should find some differences in these two sub series. Near acme, where the variability of the RR series vanishes, there are intervals in which the series is constant. This event has zero probability in our model, based on a sequence of continuous variables. In order to compare the data to the model, we have distorted the RR series adding a sequence of independent normal values with mean 0 and standard deviation 0.1. This perturbation, which is much smaller than 1, the resolution of data values, modifies the data only near the acme, since far from it the variability of the data is much greater. This perturbation has not substantially modified the interesting structure of the data, as can be seen a posteriori, since the values of the statistics in the last row of Table 1 turn out to be significantly different from the value 3/2.
In fig.3 there are the histograms of length of monotonicity intervals of a typical case. The simulated series with the same length of the RR series (second panel) has a distribution non distinguishable from the theoretical one for i.i.d. variables (first panel). The distributions of stress and recovery phases in the exercise RR sequence are different from each other and they

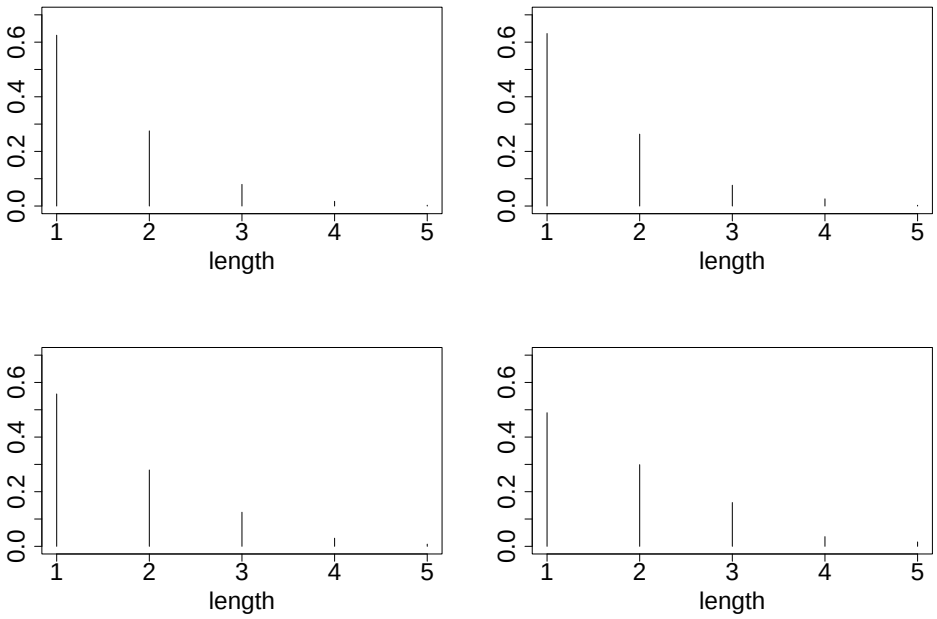

Figure 3: Distribution of length of monotonicity intervals (lengths greater than 5 are not reported). First panel (top left): the distribution for an i.i.d. sequence computed according to theory; second (top right): histogram for a simulated i.i.d. sequence with the same length of the RR sequence; third: histogram of the length of intervals in stress phase for the RR sequence; fourth: the same for recovery.

	stress		recovery	
case	inc	dec	inc	dec
1	1.76	1.84	1.74	1.97
2	1.72	1.75	1.95	1.62
3	1.66	1.87	2.29	2.67
4	1.84	1.97	2.39	1.83
5	1.95	2.03	1.97	2.01
6	1.63	1.80	2.22	2.15
7	1.87	2.20	2.18	2.08
8	1.72	1.64	2.13	1.81
9	1.76	1.99	2.02	1.75
10	2.00	2.21	2.28	2.17
11	1.78	1.81	2.29	2.36
12	1.66	1.66	1.79	1.89
13	1.63	1.85	1.94	1.95
14	1.43	1.66	1.41	1.46
	1.74	1.88	2.04	1.98

Table 1: Rounded values of the mean length of monotonicity intervals of the 14 cases. First and second columns: increasing and decreasing during stress phase; third and fourth columns: increasing and decreasing during recovery phase. In the last row there are the column means

are both different from the i.i.d. case (third and fourth panels).
In order to get a quantitative evaluation of this difference, we use as a discriminant statistics the mean interval length. We have computed this mean for increasing and decreasing intervals and for stress and recovery. The results for the 14 cases are in Table 1.
Notice that all the values, with exclusion of case 14, are larger than 1.5, which is the mean for i.i.d sequences. If we consider the i.i.d. case as a model of the absence of control on the RR sequence, this result means that the control system produces longer monotonicity intervals.
We have performed paired T test for the means of the columns; the results are in Table 2.

col. 1 and col. 2	p-value = 0.0004
col. 3 and col. 4	non significant
col. 1 and col. 3	p-value = 0.0004
col. 2 and col. 4	non significant

Table 2: Result of paired T test of comparison between the means of columns of Table 1.

Table 2 suggests that the control system acts differently in stress and recovery. During stress there is a significant difference between duration of increasing and decreasing intervals, with prevalence of the latter (first line), but during recovery the difference is not significant (second line). The duration of increasing intervals is longer in recovery than in stress (third line), but the duration of decreasing intervals is not different in the two phases (fourth line).

4 Comparison with spectral analysis

The indices usually utilized by clinicians in the analysis of heart rate variability are commonly divided into two groups: time domain and frequency domain indices[12]. Both type of indices are not designed to separate accelerations and decelerations of heart rate, hence the analysis of extrema is complementary with respect to them. The time domain indices are measures of variability of the RR sequence or of the differentiated series and are strongly influenced by non stationary behavior of the series. Using some of them it is possible to find significant differences between stress and recovery phases, but in our opinion these are mainly due to the non stationary behavior. The spectral indices are used to detect the influences of the neuroautonomic control, investigating how the variability is distributed among the frequencies. We give an example of their use. We have considered two segments of 300 heart periods of the time series: the first one is selected at the end of the stress phase,just before the acme, and the second one at the end of the recovery phase. In these two segments an exponential trend is found and the residuals are computed. We have made a spectral analysis of the residuals, focusing on the HF component of the power spectrum [10], i.e. the power spectrum over the frequencies between 0.15 Hz and 0.4 Hz.

case	end of stress	end of recovery
1	0.78	0.05
2	0.60	0.13
3	0.70	0.02
4	0.31	0.31
5	0.65	0.05
6	0.67	0.02
7	0.59	0.09
8	0.65	0.20
9	0.63	0.18
10	0.70	0.23
11	0.79	0.05
12	0.61	0.14
13	0.61	0.14
14	0.56	0.47

Table 3: Normalized HF index of the power spectrum.

We have used the normalized HF index, defined [12] as the ratio of the HF component and the total power minus the VLF component (Very Low Frequency component is defined as the power over the frequencies less than 0.04 Hz). The results are reported in Table 3. The paired T test of the two columns is highly significant (p-value is of the order of 10^{-6}). We have used the normalized index since the variances on the two segments are very different: as previously noticed, the near acme segment has a much smaller variance. According to the usual interpretation the HF index is related to parasympathetic stimulation, which is prevalent in the recovery phase and manifests in the so called Respiratory Sinus Arrhythmia. Hence one should find smaller values of HF index in the stress phase than in the recovery. The larger values of the first column are in contrast with this interpretation. A possible explanation is that the variability of the RR intervals in the first segment is largely due to measurement noise. Actually the HF index is significantly different but not far from the one of a flat spectrum, in which this index has the value $(0.4-0.15)/(0.5-0.04) \simeq 0.54$. Hence the analysis should be performed over segments which contain more variability, so that noise contamination is relatively smaller. Owing to the strong

non stationary behavior of the series, the choice of these segments is rather problematic and deserves further investigation. The analysis of extrema overcomes this problem, since it allows us to compare longer segments of the series in which the length of monotonicity intervals is almost stationary. It also complements power spectral analysis, which does not allow to separate increasing and decreasing behavior of the series. The monotonic variation series, not analyzed by us here, should contain other information, mainly regarding the non stationary behavior of the data series.

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References

[1] Balocchi R., Menicucci D., Santarcangelo E., Sebastiani L., Gemignani A., Ghelarducci B., Varanini M. (2004) "Deriving the respiratory sinus arrhythmia from the heartbeat time series using empirical mode decomposition" *Chaos Solitons & Fractals*, **20**, 171-177.

[2] Breiman L. "Probability" (1992) SIAM.

[3] Cammarota C., Guarini G., Rogora E., Ambrosini M. (2003) "Non stationary model of the heartbeat time series in atrial fibrillation" Mathematical Modelling & Computing in Biology and Medicine. Proceedings 5th ESMTB Conference 2002, V. Capasso Ed., Esculapio, Bologna.

[4] Cammarota C., Rogora E. (2006) "Spectral and symbolic analysis of heart rate during tilt test", *Phys. Rev. E* **74**, 042903-1, 042903-4.

[5] Cammarota C., Rogora E. (2007) "Time reversal, symbolic series and irreversibility of human heartbeat", *Chaos, Solitons and Fractals* **32**, 1649-1654.

[6] Costa M., Goldberger A.L., Peng C.-K. "Broken asymmetry of the human heartbeat: loss of time irreversibility in aging and disease", *Phys. Rev. Lett.* **95**, 198102 (2005).

[7] Di Garbo A., Balocchi R., Chillemi S. (1998) "Nonlinearity tests using the extrema of a time series" *Int. J. Bif Chaos* **8**, 1831-1838.

[8] Gibbons R.J., Balady G.J. et al.(1997) "ACC/AHA guidelines for exercise testing: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing)" *Circulation* **96** (1), 345.

[9] Huang N.E.,Shen Z., Long S.R., Wu M.C., Shih H.H., Zheng Q., Yen N-C., Tung C.C., Liu H.H.(1998) "The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis", *Proc.Roy.Soc. London***A454**,903-995.

[10] Malliani A., Pagani M., Lombardi F., Cerutti S. (1991) "Cardiovascular neural regulation explored in the frequency domain" Circulation **84**, 482-492.

[11] Rohatgi V. K. (1976)*An introduction to Probability Theory and Mathematical Statistics*, New York, Wiley.

[12] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) "Standard measurement, physiological interpretation and clinical use". *Circulation* **93**:1043-1065.

[13] Tateno K., Glass L., (2001) "Automatic detection of atrial fibrillation using the coefficient of variation and density histograms of RR and ΔRR intervals" *Med. Biol. Eng. Comput.* **39**664-671.

[14] Wu Z., Huang N.E. (2004) " A study of the characteristics of white noise using the empirical mode decomposition method" *Proc. Roy. Soc. London* **A460**, 1579-1611.

[15] R Development Core Team (2005). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.