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MODELING TREND AND TIME-VARYING VARIANCE OF HEART BEAT RR INTERVALS DURING STRESS TEST

CAMILLO CAMMAROTA
Mathematics Department
University La Sapienza, P.le A. Moro 2
00185 Rome, Italy
cammar@mat.uniroma1.it

MARIO CURIONE
Clinical Science Department
University La Sapienza, P.le A. Moro 2
00185 Rome, Italy
Mario.Curione@uniroma1.it

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The heart beat RR intervals extracted from the electrocardiogram recorded during the stress test show a non stationary profile consisting of a decreasing trend during the exercise phase, an increasing trend during the recovery and a global minimum (acme). In addition this time series exhibits a time-varying variance. We decompose the series into a deterministic trend and random fluctuation. The trend is obtained as an exponential fit of the data; the fluctuation is modeled as a mean reverting process driven by the trend, in which the random innovation has a time-varying variance. Data analysis, performed on ambulatory recorded electrocardiograms of 10 healthy subjects, shows that the model describes correctly the data series on a scale of at least 300 beats.

Keywords: Time series; mean reversion; heart rate variability; exercise test; heart beat; RR interval.

1. Introduction

The exercise stress test is routinely performed to evaluate the presence in the electrocardiogram (ECG) of myocardial ischemia. In the multistage Bruce protocol [1] the patient on a bicycle ergometer is subjected to a workload increasing in time by steps (25 W every 2 minutes). The exercise is stopped when the heart rate reaches a maximum, usually 85% of the estimated top heart rate based on the patient's age. After achieving peak workload, the patient spends some minutes at rest on the bicycle until his heart rate recovers its basic value. During the test 12-leads ECG is monitored and diagnosis of ischaemia is usually performed by visual inspection of the ECG signal.

The exercise induces strong modifications of the heart rate reflecting the control of the neuroautonomic system. The heart rate is measured beat-to-beat from the reciprocal of the duration of a complete cardiac cycle, defined as the interval between two consecutive R peaks in the ECG (RR interval). The RR time series recorded in the stress test shows a non stationary behavior that can be qualitatively described as follows. We refer as a typical example to Fig. 1.

(1) The RR sequence shows two different types of trend: a decreasing one during exercise (stress phase) and an increasing one during recovery (recovery phase); these two phases are separated by a global minimum (acme).
(2) The sequence shows a time dependent variability, that is larger when RR intervals are larger.

In the analysis of the heart rate time series the variability of RR intervals is known as the Heart Rate Variability (HRV) [2]. This variability is quantified by

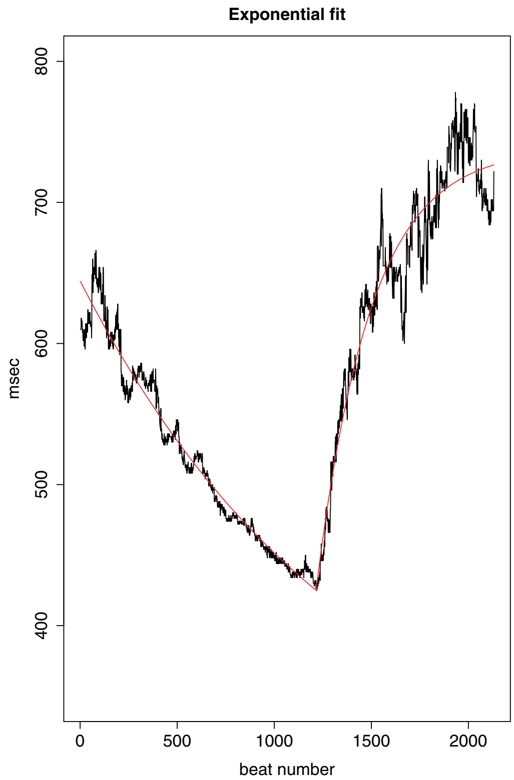

Fig. 1. Sequence of RR intervals (in msec) of a normal subject versus the beat number obtained with the Bruce protocol exercise test. The exponential trend is added.

means of several indices both in time and in frequency domain, and it is used to extract information on the control of the autonomic nervous system on heart rate. The HRV indices are usually evaluated on RR sequences recorded at rest, when the sequence can be supposed to be stationary or from 24 hours Holter monitoring, where analysis on several time scales can be performed.

Evaluation of HRV indices during exercise has been less frequently performed. In clinical studies a first type of approach focuses on the trend component of the RR intervals in recovery: a heart rate recovery of less than 12 beats per minute in the first minute was found to be a predictor of overall mortality [3]. A second approach removes baseline trend induced by exercise in the RR series using a suitable filter and then evaluates HRV on the residual. Several indices estimated over intervals of two minutes were found to be predictors of cardiovascular mortality [4]. Nevertheless the authors of [4] point out that the results during exercise contrast to results of HRV during rest, both in time and in frequency domain, concluding that the current explanations for the physiologic genesis of HRV at rest do not necessarily extend to exercise testing.

In the context of time series modeling evaluations of HRV have focused on comparison of exercise to rest. The complexity of heart rate was found to be less during and after a training camp of athletes than before [5]. In [6] differences in correlation properties are found between rest and exercise. In [7, 8], where the cardiorespiratory synchronization is investigated during, before and after exercise, it is observed a reduced variability of RR intervals and a reduction in synchronization during exercise with respect to rest.

In the experimental setting of previous papers the workload during exercise is constant in time. Data from the diagnostic protocols are characterized by a workload increasing in time. The RR time series so obtained are an example of a non stationary series for which novel mathematical techniques should be useful. A first attempt to investigate these data is in [9] where time-frequency methods of signal analysis were applied to estimate how low frequency and high frequency spectral components vary in time. In application to real data very low frequencies have been filtered out. An analysis based on a non parametric approach (analysis of extrema) is in [10]. The earlier references show the usefulness of information contained both in trend (heart rate recovery) and in residuals after detrending (time and frequency domain indices), but have not addressed the mathematical modeling of the observations in points (1) and (2) above.

The source of variability of RR intervals includes both purely stochastic components and deterministic ones related to the multiple interactions of the cardiac system of which the cardiorespiratory interaction plays a dominant role. This interaction has been widely investigated, using mathematical models, in various conditions of breathing during rest (see for instance [11]). The dynamics of RR intervals during spontaneous breathing reveal both a deterministic behavior in the so-called "angular component", and a random one in the "radial component" [12]. According to the results in [8] the cardiorespiratory interaction is reduced during the exercise (constant workload of 50 Watt) with respect to rest, so that when the workload is increasing its contribution to the RR variability should be even smaller. In addition the strong deterministic trend in data recorded during increasing workload can mask the other sources of variability in RR series, modeled as low-frequency noise in [8].

So it is natural to consider a stochastic model for the fluctuations as a candidate to describe some other features of the RR series as the time dependent variability (point (2) above). This time dependent variability was already observed in atrial fibrillation as a dependence of the RR variance on the RR mean in 24 hours Holter recording ([13, 14]). The time varying variance has been used in [15] to model volatility in non stationary financial series. Stochastic models of RR fluctuations have been recently used in different situations ([16, 17]). As to point (1) mathematical models of non stationary series include the notion of "mean reversion", widely used to model the economic time series (see for instance [18]).

The first aim of the present report is to formulate a model of the RR sequence that explains the observations (1) and (2) above. We use the classical theory of time series [19] based on the decomposition of the series in two main components: deterministic trend and stochastic fluctuations. The model can be summarized as follows:

- The trend is obtained using a simple mechanical model related to the workload.
- The stochastic fluctuations are modeled by a mean reverting process driven by the trend.
- The time varying variance is modeled using a random innovation whose amplitude is modulated by a smooth time varying scale factor.

The second aim is to describe the series using a small number of parameters obtained from the model, that could be used to improve the diagnostic. Accordingly model estimation and validation is performed on real data series extracted during the routine ambulatory stress test. In this report we analyze 10 normal subjects who underwent to the test performed according to the Bruce protocol.

2. The Model

We model the observed RR time series as the realization of a sequence of continuous random variables (r.v.) $X_1, \ldots, X_n$, where X_t denotes the RR interval at the tth beat. The model is defined according to the following dynamical equation:

$$\Delta X_t = -k(X_t - \alpha_t) + \sigma_t \epsilon_t; \quad t = 1, 2, \ldots, t_2 - 1. \tag{1}$$

Here Δ is the difference operator, $\Delta X_t = X_{t+1} - X_t$, k is a positive constant, the sequences α_t and σ_t are, respectively, the trend and the time-varying variance and t_2 is the number of beats. Both α_t and σ_t are to be considered slowly variable at a small time scale (few beats). The stochastic fluctuation is defined by ϵ_t, a sequence of independent and identically distributed (i.i.d.) r.v. with zero mean. The model is constructed starting from a basic random walk of equation $\Delta X_t = \sigma\epsilon_t$, with addition of a mean reversion term, $-k(X_t - \alpha_t)$, that drives the random walk towards the deterministic trend α_t. The scale factor σ_t models the time-varying variance.

Given the initial value X_1 and the values of the parameters the equation defines a data generating process that can simulate the system. Equation (1) is a finite difference stochastic equation of Langevin type. The investigation of its theoretical properties is outside the scope of the present report and it is to our knowledge, not easy. We now consider in detail the components of the model.

2.1. *Trend*

The RR series shows a global minimum called "acme" whose value is denoted m. We define as "stress phase" the sequence of beats before the acme and as "recovery phase" the ones after the acme. The duration of the stress phase is t_1 beats; the global duration is t_2 beats; typical values are $t_1 = 1500, t_2 = 2500$ (see Table 1).

We model the trend as a function $\alpha(t)$, solution of a differential equation, where t is a real number in the interval $[0, t_2]$. Both phases are characterized by a restoring term that drives the system towards an equilibrium value M. For sake of simplicity we assume that this term is linear: $-a(\alpha - M)$, where a is a positive constant. Since the two phases may be characterized by different values, we shall use the notations a_1, a_2, M_1, M_2. In addition the stress phase is characterized by a constant negative contribution $-b$, that quantifies the workload and produces a decreasing of the RR intervals. We assume $\alpha(t)$ to be solution of the two following ordinary differential equations in different time intervals

$$\begin{aligned} \alpha_1' &= -a_1(\alpha_1 - M_1) - b \\ \alpha_1(0) &= M_1; \quad t \in [0, t_1], \end{aligned} \tag{2}$$

Table 1. Parameters of the RR series: from left: t_1 duration in beats of the stress phase, t_2 total duration in beats of the test, m minimum RR in msec, M_1 maximum RR in stress in msec, M_2 maximum RR in recovery in msec.

t_1	t_2	m	M_1	M_2
1218	2373	377	665	701
2021	3223	331	534	593
1601	2662	383	749	679
2094	3217	342	571	597
2098	2883	369	814	642
1303	2213	418	855	762
1225	2459	389	634	544
1147	2062	395	678	723
1219	2131	421	610	696
2030	3097	365	492	594

$$\begin{aligned} \alpha_2' &= -a_2(\alpha_2 - M_2) \\ \alpha_2(0) &= m; \quad t \in [t_1, t_2]. \end{aligned} \tag{3}$$

These equations have exponential solutions:

$$\alpha(t) = \begin{cases} M_1 - \dfrac{b}{a_1}(1 - e^{-a_1 t}), & t \in [0, t_1], \\ M_2 + (m - M_2)e^{-a_2(t-t_1)}, & t \in [t_1, t_2]. \end{cases} \tag{4}$$

Obviously we cannot solve explicitly Eqs. (2) and (3) since we do not know the values of the parameters. We estimate these parameters fitting the data series by the formula in Eq. (4). This will be accomplished in Sec. 3, and the value of the fit for each $t = 1, 2, \ldots, t_2$ is denoted α_t. An example of this exponential trend is in Fig. 1.

2.2. *Mean reversion*

The role of the mean reversion term $-k(X_t - \alpha_t)$ is to drive the system towards the deterministic trend α_t. For instance if the random innovations put the system above α_t the subsequent increment ΔX_t is negative. The coefficient $k > 0$ measures the speed of reversion. The estimate of this parameter can be done only after having estimated the trend α_t. More precisely we consider as an independent variable the values $X_t - \alpha_t$ and as a dependent one the values ΔX_t (since the sequence ΔX_t has an element less than $X_t - \alpha_t$ we cut the last element of the latter). From the scatter plot of the points defined, the slope of the linear fit gives an estimate of the parameter k. Of course for the validation of the model one has to verify that the intercept coefficient is not significantly different from zero, while the slope is a negative number significantly different from zero. This term can explain the large fluctuations around the trend that are mainly observed for large RR (Fig. 1).

2.3. *Time-varying variance*

After having estimated the parameter k, we define the sequence

$$\eta_t = \Delta X_t + k(X_t - \alpha_t), \tag{5}$$

so Eq. (1) becomes

$$\eta_t = \sigma_t \epsilon_t. \tag{6}$$

Squaring and taking logarithms we get

$$\log(\eta_t^2) = \log(\sigma_t^2) + \log(\epsilon_t^2). \tag{7}$$

Examples of sequences η_t and $\log(\eta_t^2)$ are in Fig. 2 (first and second panels, where only the stress phase is reported). From the plot of $\log(\eta_t^2)$ we argue that a linear regression with respect to time is reasonable:

$$\log(\eta_t^2) = c + dt + \gamma_t, \tag{8}$$

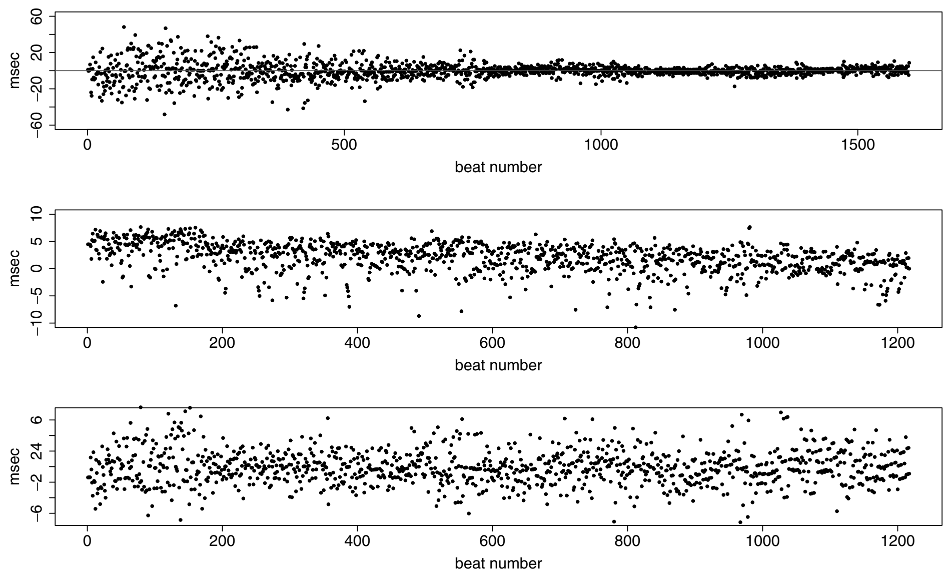

Fig. 2. Stress phase. First panel: The η_t sequence; second panel: $\log(\eta_t^2)$; third panel ϵ_t.

where c and d are constants coefficients and γ_t represents the random error term. We estimate the coefficients using the standard least squares method (Table 2). We are mainly interested in the sign of d, since $d < 0$ (in the stress phase) implies (see below) that the scale function σ_t is decreasing in time (during stress), as expected. The data points (Fig. 2, second panel) are not symmetrically distributed around the linear fit, or in other words the distribution of γ_t is not symmetric around zero. In presence of a departure from normality we are not able to compute a confidence interval of d using standard methods; this point is outside the scope of the paper.

Table 2. Estimated parameters of the model: stress (left) and recovery (right). From the left in stress: a_1 speed of reversion to equilibrium (beat^{-1}), b workload (msec/beat), k_1 speed of reversion to trend (adimensional), c_1 intercept (adimensional) and d_1 slope (adimensional) of logarithmic time varying variance, e_1 standard deviation of the error term (msec). From the left in recovery: the same without workload.

a_1	b	k_1	c_1	d_1	e_1	a_2	k_2	c_2	d_2	e_2
0.00036	0.36	−0.16	3.82	−0.0030	2.49	0.0040	−0.20	1.99	0.0006	2.12
0.00084	0.24	−0.14	1.43	−0.0003	2.46	0.0021	−0.14	−0.37	0.0010	2.19
0.00096	0.53	−0.08	4.11	−0.0025	2.27	0.0022	−0.13	−1.26	0.0019	2.30
0.00024	0.18	−0.05	3.70	−0.0024	2.53	0.0018	−0.14	−1.41	0.0012	2.17
0.00073	0.43	−0.12	4.62	−0.0025	2.32	0.0004	−0.08	−4.28	0.0025	2.31
0.00053	0.43	−0.51	4.42	−0.0037	2.15	0.0030	−0.16	0.69	0.0011	2.29
0.00038	0.25	−0.21	4.36	−0.0041	2.25	0.0044	−0.18	0.93	0.0006	2.86
0.00028	0.32	−0.14	2.86	−0.0016	2.23	0.0062	−0.17	2.97	0.0003	2.12
0.00071	0.27	−0.08	2.44	−0.0025	2.39	0.0036	−0.09	0.27	0.0013	2.81
0.00021	0.16	−0.05	3.19	−0.0016	2.34	0.0037	−0.15	−0.84	0.0013	2.74

Hence we get

$$\sigma_t = e^{\frac{1}{2}(c+dt)} \quad \epsilon_t = e^{\frac{1}{2}\gamma_t}\mathrm{sgn}(\eta_t). \tag{9}$$

Notice that the square of η_t in Eq. (7) causes to lose the information on the sign of ϵ_t; the sign is recovered from η_t in Eq. (6). One could choose ϵ_t of unit variance just dividing for its standard deviation, after having estimated it; consequently the scale function σ_t should be multiplied by this constant.

3. Estimation of the Parameters and Data Analysis

For the aims of the present study we have selected 10 healthy subjects from a group referred for symptoms and signs suggestive of myocardial ischemia to ECG Laboratory during a recent study [20]. They underwent clinical examinations and scintigraphy; the standard 12-leads ECG was recorded during all the Bruce protocol exercise test. It was used PC-ECG 1200 (Norav Medical Ltd.), which provides in output digital signal with resolution of 2.441 μV and 500 Hz sampling frequency. The duration of the test was about ten minutes both for stress and recovery. These two durations are conditioned by two factors: the heart rate and the physical performance of the patient; evaluation of possible dependency between the two durations was outside the aims of the present work.

Pre-processing was performed on the raw data. For the RR extraction the precordial lead V5 was chosen, because it is less influenced by motion artifacts. The R peak detection was performed using a derivative-threshold algorithm. Ectopic beats were absent or less than 1% of the total beats for each subject. Some missed beats produced RR intervals outside the normal range. A filtering algorithm replaced these intervals with the median computed over blocks of 30 adjacent beats. In our study we have adopted the usual method in HRV literature to consider the beat number and not the real time as the independent variable in the RR time series. The real time scale of the experiment can be recovered from the RR series, just by summation of the RR intervals.

Analysis of raw data, R peak detection, and subsequent computations were performed using the free statistical software R [21].

The parameters m, M_1, M_2, t_1, t_2 are estimated just by observation of the time series. In particular M_1, M_2 are estimated by the mean of 20 values of the series at the start of exercise and at the end of recovery, respectively. A more subtile point is the estimation of the acme, and, in particular, of the beat number t_1. To do this the RR series is smoothed so that there is only one beat in which the series takes its minimum and this defines uniquely t_1. These values are reported in Table 1.

The parameters a_1, a_2, b are not observable directly and have to be estimated from the model. From Eq. (4) a rough estimate of the parameters a_1, a_2, b can be obtained. These values are then used as starting ones in a nonlinear least squares estimation of the same parameters from the data series. The values obtained are reported in Table 2. The exponential fitting obtained is satisfactory in all the cases considered; a typical one is in Fig. 1.

The parameter k is estimated as the slope of a linear fit of ΔX_t with respect to $X_t - \alpha_t$. From the fitting report this slope is negative with a very high level of significance; the intercept is not significantly different from zero. In the estimation of the time-varying variance parameters of Eq. (8) the main parameter d is significantly different from zero.

The last parameter is the standard deviation of ϵ_t, denoted e, which represents the amount of random noise contained in the data. The values of the parameters k_1, c_1, d_1, e_1 for stress and the corresponding ones for recovery are reported in Table 2.

4. Model Diagnostics

The analysis of the residuals ϵ_t shows at least qualitatively symmetry with respect to zero, which is compatible with the hypothesis of zero mean (Fig. 2, third panel); the quantile-quantile plot of the non normalized distribution versus a standard normal (Fig. 3, first panel) shows a moderate departure from normality.

In order to test the assumption of independence of ϵ_t, we have used the standard methods of statistical time series analysis, for which we refer for instance to [19]. We have first extracted sub series of ϵ_t of 300 beats located in the middle of stress and

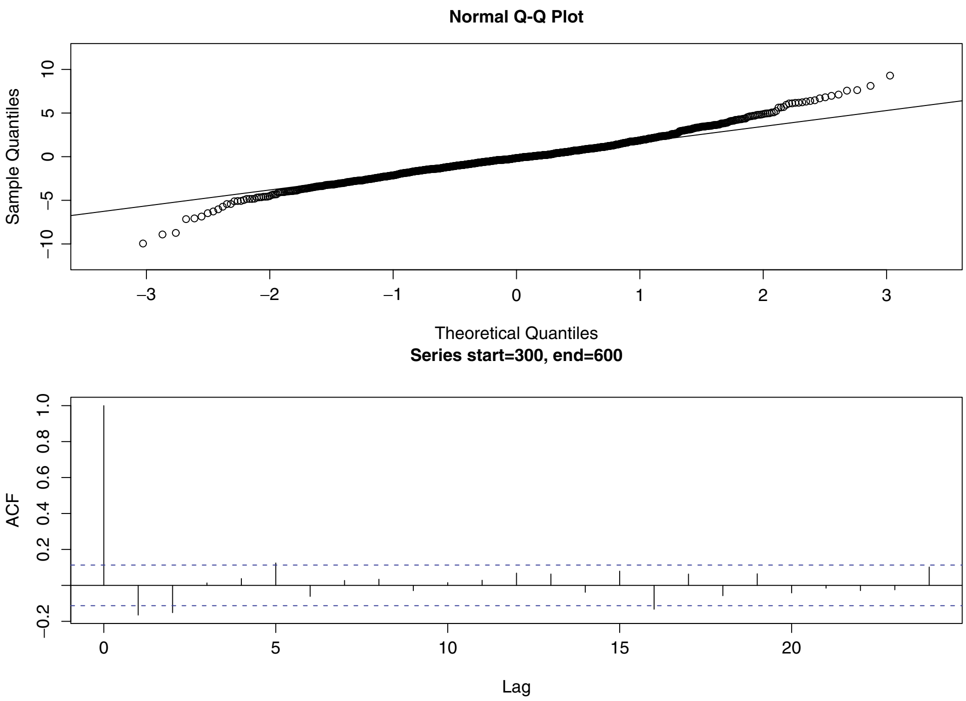

Fig. 3. Stress phase. First panel: The normal Q-Q plot of the sequence ϵ_t; second panel: the autocorrelation function of ϵ_t for a segment of 300 beats.

recovery phases. For these sub series we have computed the autocorrelation function (ACF). The plot of a typical ACF (Fig. 3, second panel) shows that the majority of the values are inside the 95% confidence limits (dashed lines) and that only a few values are nearly outside. In these cases it is usual not to reject the assumption that the sequence is uncorrelated. In some nonlinear models of time series (for instance, ARCH models of financial series) there is the following situation: the series is not independent; the series has zero ACF; the squared series has non zero ACF. For this reason we have computed the ACF of the sub series ϵ_t^2; the results are similar to the ones of ϵ_t and we conclude that also the ACF of the sub series of ϵ_t^2 is zero. This rules out the possibility of this type of nonlinear models. We have also tested the stronger assumption that the subseries ϵ_t is an independent sequence. We have used the runs test, a non parametric test that does not assume normality. The runs test shows that the independence cannot be rejected at the 95% confidence level. Hence we conclude that at least on the chosen temporal windows of 300 beats, the i.i.d. assumption cannot be rejected.

The same tests for the entire series ϵ_t (not reported here) show a significant departure from the i.i.d. assumptions. We conjecture that this is caused by non stationary behavior that is still present, if much reduced, and that cannot be explained by the model. This behavior depends on several factors. The first one is the departure of individuals features from the model, in particular for the exponential trend, that is typical of medical data. A second one is the low resolution of the RR interval measurement. Actually the RR values close to acme, where the variability is smaller, have a very small range and are more similar to discrete r.v. than to continuous ones. This can be seen at the right end of the ϵ_t plot in the third panel of Fig. 2. A third one is the cardiorespiratory interaction, that may modulate the variability at the beginning of exercise and at the end of recovery (larger RR values).

At this stage of our findings the independence of the entire sequence ϵ_t can be assumed in the model defined by Eq. (1) only as a first approximation.

5. Conclusion

In our model of the RR series the trend is described by a simple (exponential) sequence, and the fluctuations are decomposed into two contributions: the time varying variance and the error term. The first one is in turn a simple (exponential) scale factor and the second one is modeled as a random sequence. The model uses a small number of parameters that describe some relevant features of the series, if compared to the complexity of this type of data. The parameters of trend and time varying variance reported in Table 2 show that there is an inter individual variability, but this is in the typical range of medical data. Some essential parameters that quantify the main features are rather homogeneous both in sign and in value.

The tests on the random sequence ϵ_t show that over some intervals of 300 beats this sequence can be considered as an independent sequence of r.v. Hence at this stage the main information contained in this sequence are the two standard deviations e_1, e_2 of stress and recovery in Table 2 . We notice that these are rather constant in the group of individuals, which is surprising in medical data.

The modeling of ϵ_t as an independent random sequence cannot be extended to all the duration of the test. In particular for larger RR intervals we expect that the interaction of respiratory and other systems modulates the RR variability. This would be reflected in a non zero autocorrelation of ϵ_t; but to observe it one should have sufficiently long stationary conditions. This experimental setting characterized by a strong trend masks these modulations. It is not excluded that for larger RR intervals a more detailed analysis aimed to point out the deterministic behavior as the one in [12] could reveal the cardiorespiratory interaction.

Our results show that a great part of the information is contained in the non stationary behavior, i.e., the profiles of trend and time-varying variance. In those HRV studies, where indices are computed on the residuals obtained after detrending, a bias is introduced since there is another source of non stationarity, i.e., these residuals are non stationary in variance. This could explain the controversial results in [4].

While the actual clinical use of the stress test consists mainly in a visual inspection of the ECG, the model provides a set of parameters that could lead to new clinical applications. Each comparison of a parameter during stress with the corresponding one during recovery could be interesting. For instance parameters a_1 and a_2 reflect the restoring force towards equilibrium in stress and recovery. These two phases are respectively prevalently under the influence of the sympathetic and vagal termination of neuroautonomic system, so that the parameters should provide a quantification of these influences. The same for the pairs k_1, k_2 and e_1, e_2 to which a physiologic meaning should be given. We have described the stepwise loading by a unique constant parameter, as a first approximation. A more accurate use of timing of the load and of the response could also provide interesting informations. A comparison between normal of the non normal cases could provide useful insights for instance in diagnosis of ischaemia. In these type of investigations a larger number of cases than the present one is required.

Acknowledgments

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