TIME DELAY BETWEEN RR AND RT HEART BEAT INTERVALS ASSESSED BY TREND EXTRACTION OF EXERCISE TEST DATA

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

Received (received date)
Revised (revised date)

The RR and RT time intervals extracted from the electrocardiogram measure respectively the duration of cardiac cycle and repolarization. The series of these intervals recorded during the exercise test are characterized by two trends: a decreasing one during the stress phase and an increasing one during the recovery, separated by a global minimum. We model these series as a sum of a deterministic trend and random fluctuations, and estimate the trend using methods of curve extraction: running mean, polynomial fit, multi scale wavelet decomposition. We estimate the minimum location from the trend. Data analysis performed on a group of 20 healthy subjects provides evidence that the minimum of the RR series precedes the minimum of the RT series, with a time delay of about 19 seconds.

Keywords: ECG, trend, time delay, time series, wavelets, multiresolution, minimum, RR interval, RT interval, heart rate variability, exercise test.

1. Introduction

From the electrocardiogram (ECG) several time intervals can be measured, revealing important informations on the heart function. The R peak of ECG (fig.1) corresponds to systole and the time interval between two consecutive R peaks (RR interval) is a measure of the duration of a complete cardiac cycle, corresponding to the instantaneous heart rate. During exercise the RR intervals are shorter than at rest (fig.1 top and bottom) and they take a minimum at the maximal exercise (acme). The time interval between the Q wave and the end of T wave (QT interval) reflects the overall duration of the ventricular repolarization. The existence of a relationship between these two intervals was recognized and used in clinical applications: the QT value is 'corrected' basing on the previous RR value (see for instance [7]). During exercise the peak of the T wave is adopted instead of the end

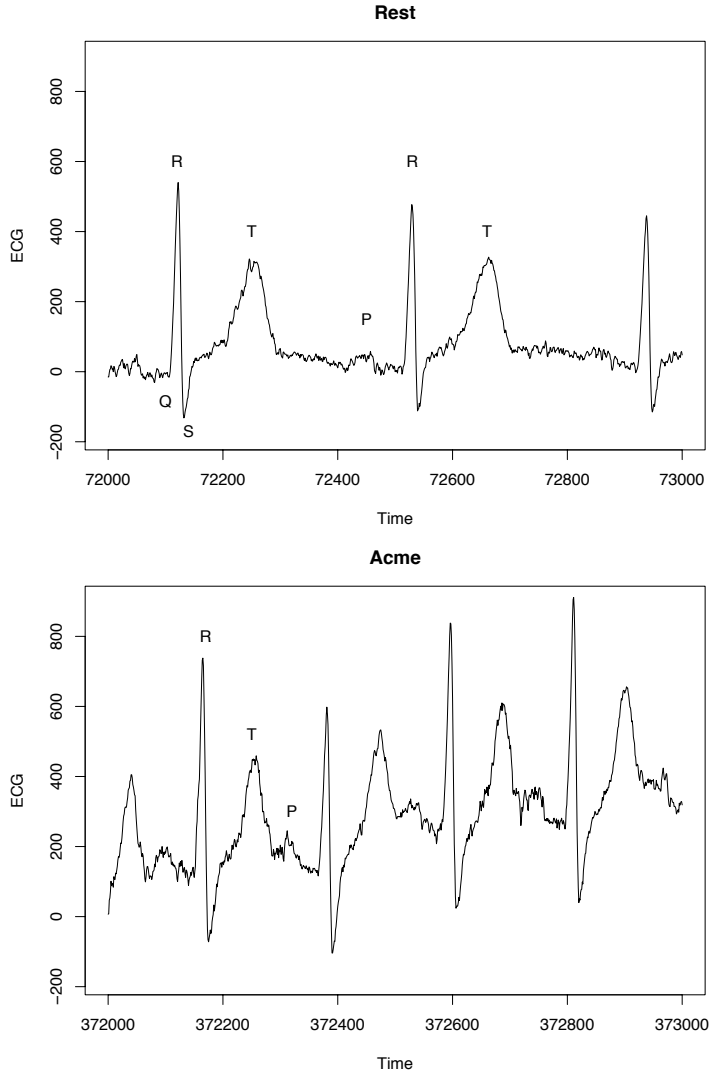

Fig. 1. Two seconds recording of the ECG during exercise test (raw data from the lead V5). Top: The ECG signal at the start of the test (rest condition) with the R peak and the apex of T wave. Bottom: the signal at the acme, when the RR interval takes its minimum. Time unit = 0.002 sec; ECG voltage resolution unit= 2.441 microVolt.

of the T wave because the latter is not reliable at rapid heart rates in which the T wave fuses with the ensuing P wave (fig.1, bottom). The major component of the QT interval changing with exercise is the interval from onset of the QRS complex to the peak of the T wave. Terminal repolarization (peak to end of T wave) does not shorten with exercise [10, 12]. It is possible to consider as an equivalent index

of repolarization, in place of QT, the duration of the RT interval, defined as the time between the R peak and the apex of T wave.

It was observed that following an abrupt change in RR duration the RT adaptation is not immediate and a time delay exists [13]. In a small group of non healthy patients the typical values of time delay were estimated to be in different conditions 136 and 189 seconds. A more recent investigation of the time delay was conducted over patients survivors of acute myocardial infarction using 24 hours Holter recordings [20]. This estimate was based on a mathematical model that assumed a dependence of the RT interval on the weighted mean of several previous RR intervals. The time of adaptation was estimated to be 150 beats, corresponding to 2.36 minutes, with large inter individual variability. In [19] a model of the RR-RT interaction was used to estimate the coupling parameters in stationary conditions, assuming that the RT interval depends on previous RR intervals.

In above models the parameters estimation, included the time delay, is based on the assumption that between RR and RT series an unidirectional coupling exists, where the RR-RT casual relationship is of type driver-response. In other words in the interaction of the two series the RT value depends on previous RR values. In biological time series various methods have been adopted to detect coupling directions and to estimate delays. These methods generally assume that the series are stationary or moderately non stationary. In physiological signals we refer to [22] for cardiorespiratory interaction, to [24] and [8] for interaction between heart rate and blood pressure.

One of the settings in which RR and RT intervals are progressively varied is the exercise test, that is routinely performed to evaluate the presence in the ECG of myocardial ischemia [9,15]. The RR series shows a non stationary behavior that can be qualitatively described as a V shape profile (we refer as a typical example to fig. 2 (top)): a decreasing trend during exercise (stress phase) and an increasing one during recovery (recovery phase); these two phases are separated by a global minimum (acme). According to a model proposed in [3] these two phases can be described by exponential trends and the fluctuation has a time varying variance. An analysis of local extrema is in [2]. The RT time series has the same type of trend, as it is shown in fig. 2 (bottom). At our knowledge a model is not existing for RT series; a visual inspection of fig. 2 suggests that the two series differ for the amount of fluctuation. We also notice that both series exhibit an asymmetry with respect to acme, i.e. the slope at the early stage of recovery is larger than the one at the end of stress (fig. 2). For these series it was observed that for a given RR interval the RT interval is shorter during recovery than during stress (hysteresis) [4,12,14]. Obviously hysteresis can be explained if one assumes that the RT interval responds slowly to changes in heart rate.

In the present paper we firstly consider the trend estimation of the RR and RT series during the exercise test. We use standard methods of curve extraction as the running mean and the polynomial fitting [1], and a wavelet multiresolution analysis. For a general reference on the use of wavelets in time series see [17]. Wavelets

are used for extraction of trend in physiological time series [16] and in statistical problems [5]. Physiological time series are frequently described using a multi-scale approach and the wavelet transform provides a simple and clear method for separating the scale contributions. A wavelet method was used to extract variability indices for non stationary RR time series in various situations [18], [23]. For a different approach (detrended fluctuation analysis) to RR series of exercise and recovery see [11].

The second aim of the present paper is to provide evidence of a time delay between RR and RT intervals, that is independent on any coupling assumption between the two series, and to give an estimate of it. At this aim we exploit the experimental setting provided by the exercise test, during which both series take a minimum: we estimate the time delay as the time distance between the two minima.

The above mentioned methods of trend estimation are characterized by different assumptions on the type of trend and by restrictive assumptions on the fluctuation. We analyze the residuals of the series after detrending in order to verify the validity of these assumptions and discuss their relevance.

2. Data acquisition

In multistage Bruce protocol [9] 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 its heart rate recovers its basic value. The standard 12-leads ECG was recorded using the electrocardiograph PC-ECG 1200 (Norav Medical Ltd.), which provides in output digital signal with resolution of 2.441μV and 500 Hz sampling frequency. The duration of the test was about ten minutes both for stress and recovery.

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. The T apex was detected as the maximum of the T wave subsequent to each R peak. 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. We have analyzed 20 normal subjects who underwent to the test performed according to the Bruce protocol in a preceding study of our group [6]. Analysis of raw data, R and T peak detection and subsequent computations were performed using the free statistical software `R` [21].

3. Trend extraction

We assume as a model for both RR and RT series, denoted $X_t, t = 0, ..., N-1$, the following one

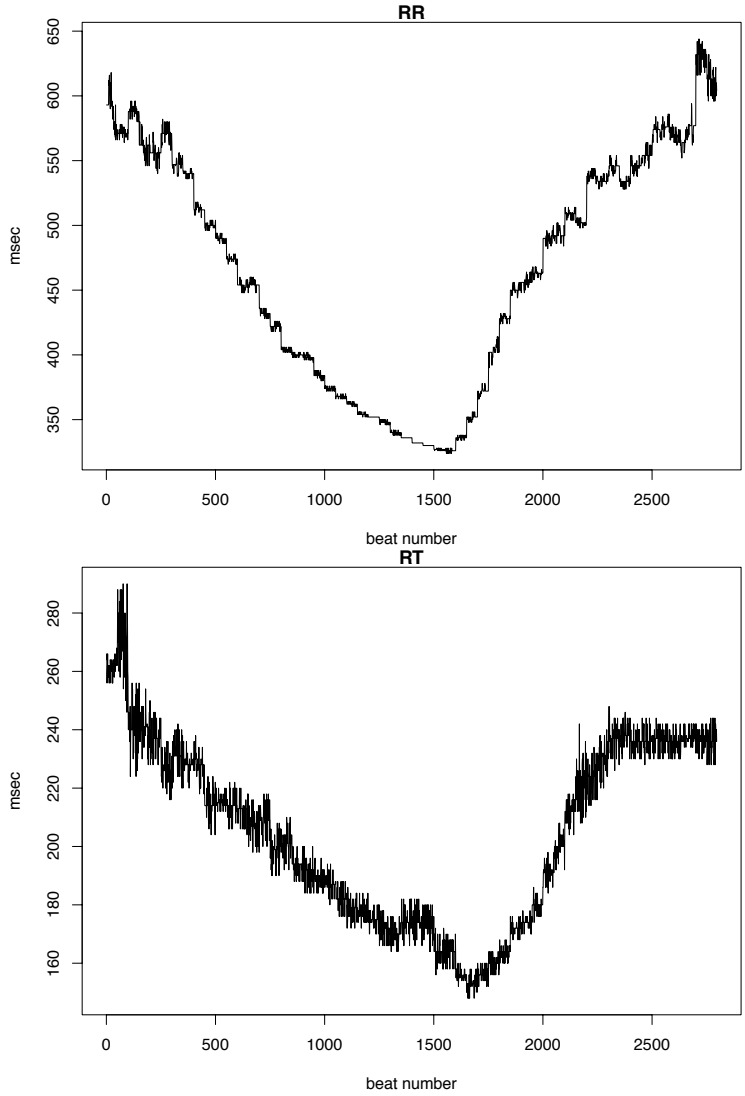

Fig. 2. The RR (top) and RT (bottom) time series of the same subject during the exercise test. Unit of RR and RT interval is millisecond.

$$X_t = T_t + \epsilon_t \tag{1}$$

where T_t denotes a deterministic sequence (trend) and ϵ_t a sequence of random variables (fluctuation). At the present there is no generally accepted model for trend and fluctuation of the RR series during exercise, and we are not aware of any previous investigation on RT. In [3] on the basis of a dynamical model the trend

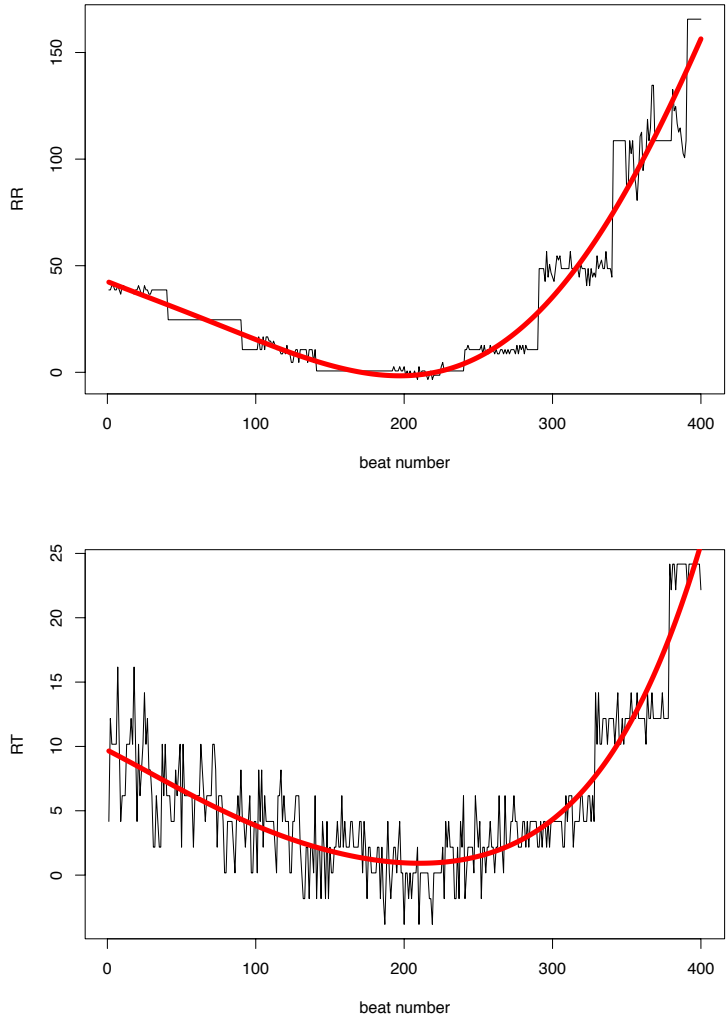

Fig. 3. Windows of 400 beats of RR and RT intervals (in millisecond) around the minimum previously estimated and polynomial trend (color on line).

of RR was assumed to be a decreasing exponential during the stress phase and an increasing one during recovery. This global model for trend did not provide any information on the acme, which is the object of the present investigation. The level of fluctuation of the RR series is variable in time and it is negligible close to the acme (fig. 2, top). On the contrary in RT series the level of fluctuation appears to be constant and non negligible (fig. 2, bottom). This fluctuation is mainly due to

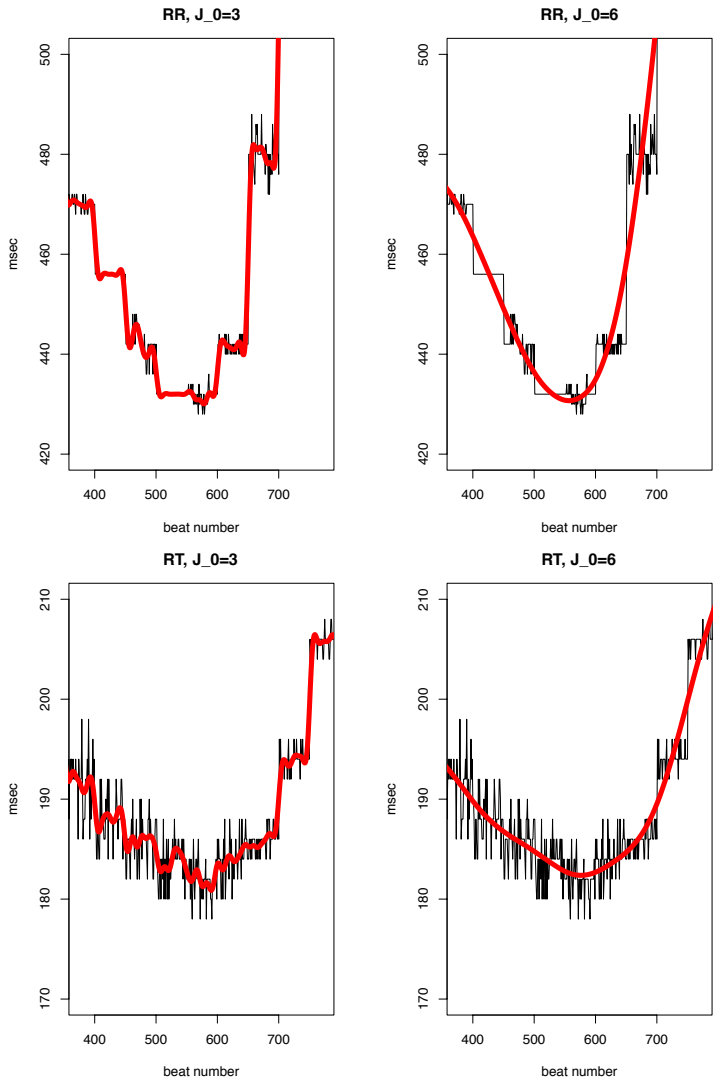

Fig. 4. Top left : RR duration (in millisecond) and smooth (color on line), versus beat number; bottom left: corresponding RT duration (in ms) and smooth, versus beat number. The levels of smooth are $J_0 = 3$ left and $J_0 = 6$ right.

the errors in the measurement of the apex of the T wave, which is not so sharp as the R peak (see an example in fig. 1 top, at the first T wave). Furthermore some of the series in our database show an asymmetry close to the acme: the slope is greater at the start of the recovery phase than at the end of the stress (see fig. 2).

We consider the problem of estimating T_t assuming that it has only one global

minimum (acme). The sequence ϵ_t is assumed to be a stationary sequence of independent normal variables of zero mean and variance σ^2. In the sequel we discuss the applicability of these assumptions. We use three methods for trend extraction: running mean, polynomial fit and wavelet analysis.

The running mean provides an estimator of the trend T_t given by

$$\hat{T}_t = \frac{1}{2n+1} \sum_{i=-n}^{n} X_{t+i} \tag{2}$$

In case of a linear trend, $T_t = a_0 + a_1 t$, this estimator is non biased, i.e. $\mathbb{E}(\hat{T}_t) = T_t$ and its variance is $\mathbb{V}ar(\hat{T}_t) = \sigma^2/(2n+1)$. In case of a quadratic profile, $T_t = a_0(t-c)^2$, one easily gets

$$\hat{T}_t = a_0(t-c)^2 + \frac{a_0}{2n+1} \sum_{i=-n}^{n} i^2 + \frac{1}{2n+1} \sum_{i=-n}^{n} \epsilon_{t+i} \tag{3}$$

$$\mathbb{E}(\hat{T}_t) \approx a_0(t-c)^2 + a_0 \frac{n^2}{3}; \qquad \mathbb{V}ar(\hat{T}_t) = \frac{\sigma^2}{2n+1} \tag{4}$$

where we have considered only the leading term in n.

We notice that the bias of the estimator $\hat{T}_t$, i.e. $a_0 n^2/3$, is a constant independent on t and so the minimum location can be estimated correctly, although the minimum value is not. The squared risk R^2 of this estimator, defined as the squared bias plus variance, is approximately for large n

$$R^2 \approx (a_0 \frac{n^2}{3})^2 + \frac{\sigma^2}{2n}$$

This, considered as a function of n, takes its minimum at

$$\overline{n} = \left(\frac{9}{8} \frac{\sigma^2}{a_0^2} \right)^{\frac{1}{5}} \tag{5}$$

Obviously one needs to know the standard deviation σ and the convexity parameter a_0 to compute $\overline{n}$. We consider these problems below.

The case more realistic of a non symmetric profile close to the minimum is not easy and requires suitable assumptions on the type of asymmetry. This case, that is outside the scope of the present paper, at our knowledge is not discussed in literature.

We have investigated the dependence of the minimum location on the length of the filter for the values $n = 4, 8, 16, 32$. The results are reported in Tab. 1.

A polynomial trend model that includes the information of the presence of a minimum can be defined as follows

$$T_t = b + (t-c)^2(a_0 + a_1 t + a_2 t^2 + a_3 t^3) \tag{6}$$

We have used the non linear least squares fitting `nls()` function of `R` in a window of the data centered at the minimum previously estimated of total length 400 beats and with subtraction of the minimum (fig. 3). We have preferred this non linear fitting algorithm to a standard polynomial one, because the former allows to extract more directly the interesting parameter c of minimum location.

The function `nls()` requires starting values for the parameters in order to get an optimal convergence of the algorithm. We have used $c = 200; a_0 = 0.01; b = a_1 = a_2 = a_3 = 0$. The results are in the table 2.

In this table the columns 1 and 5 contain the estimate of the parameter c, i.e. the minimum location of RR and RT series. The columns 2 and 6 contain the standard error of the minimum locations (the means are 3.0 and 5.7). The columns 3 and 7 contain the estimate of parameter a_0, related to the convexity of the trend profile. The columns 4 and 8 contain the residual standard error, which provide an estimate of the parameter σ.

We can compute the optimal value of n, related to the length of the filter according to eq. (5) for each case, using the values of a_0 and c provided by table 2. The mean value of $\overline{n}$ turns out to be 43 for RR and 56 for RT. These values are optimal if the profile of the minimum is parabolic. Some of our series have an asymmetric profile, and so we can only conjecture that a smaller width of the filter should reduce the squared bias. The value $n = 32$ of table 1 seems to be a good compromise.

The third method we use for the extraction of the trend is based on wavelets. In the notations of [17] the discrete wavelet transform (DWT) of

$$\mathbf{X} = (X_0, ..., X_{N-1})$$

where N is a power of 2, is a vector of wavelet coefficients

$$\mathbf{W} = (W_0, ..., W_{N-1})$$

that is composed of $J_0 + 1$ subvectors,

$$\mathbf{W} = (\mathbf{W}_1, ..., \mathbf{W}_{J_0}, \mathbf{V}_{J_0}),\ 2^{J_0} \leq N$$

where $\mathbf{W}_j$ has $N/2^j$ elements, and such that each of them can be associated with a particular scale: $\tau_j = 2^{j-1}$ in case of $\mathbf{W}_j$ and $\lambda_{J_0} = 2^{J_0}$ in case of $\mathbf{V}_{J_0}$. An analysis of variance (ANOVA, or energy decomposition) holds

$$||\mathbf{X}||^2 = \sum_{j=1}^{J_0} ||\mathbf{W}_j||^2 + ||\mathbf{V}_{J_0}||^2 \tag{7}$$

where

$$||\mathbf{X}||^2 = \sum_{t=0}^{N-1} |X_t|^2$$

Table 1. Running mean estimation of minimum location of RR and RT series of 20 normal subjects, at four increasing filter lengths $2n+1$. The last line contains means and standard deviations of minimum locations differences.

$n=4$		$n=8$		$n=16$		$n=32$	
RR	RT	RR	RT	RR	RT	RR	RT
967	877	962	1029	967	1032	967	1032
1367	1455	1364	1459	1370	1451	1370	1451
817	808	813	812	806	823	806	823
579	574	576	583	568	583	568	583
1206	1295	1213	1291	1218	1284	1218	1284
1961	2033	1993	2038	1976	2030	1976	2030
2091	2231	2088	2182	2080	2183	2080	2183
2029	2150	2024	2140	2030	2138	2030	2138
1255	1245	1259	1241	1267	1234	1267	1234
1378	1358	1379	1359	1383	1367	1383	1367
2072	2288	2089	2292	2081	2282	2081	2282
1562	1660	1566	1658	1573	1671	1573	1671
786	1016	788	1012	783	1017	783	1017
1205	1293	1209	1284	1217	1276	1217	1276
1219	1187	1216	1161	1217	1164	1217	1164
1155	1045	1159	1131	1167	1133	1167	1133
1039	1105	1035	1117	1034	1120	1034	1120
1869	1924	1873	1927	1878	1935	1878	1935
1032	1072	1027	1068	1020	1066	1020	1066
1405	1445	1409	1441	1417	1431	1417	1431
53 ± 88		59 ± 71		58 ± 72		58 ± 72	

In this paper we use the multiresolution analysis (MRA) of $\mathbf{X}$, an additive decomposition in terms of the N dimensional vectors $\mathbf{D}_j$ (the jth level detail, $1 \leq j \leq J_0$) and $\mathbf{S}_{J_0}$ (the J_0th level smooth), associated with scales τ_j in case of $\mathbf{D}_j$ and λ_{J_0} in case of $\mathbf{S}_{J_0}$. The time series is decomposed according to

$$X_t = \sum_{j=1}^{J_0} D_{j,t} + S_{J_0,t} \tag{8}$$

We base the MRA on the non dyadic wavelet transform called 'maximal overlap' DWT (MODWT). In dyadic DWT the coefficients are computed over rigidly fixed intervals that not necessarily line up with interesting features of the time series, as the minimum. In MODWT the transform is shift invariant, which allows a optimal detection of the minimum at each scale. The wavelet filter is LA(8), Daubechies least asymmetric scaling filter with 8 coefficients, and periodic boundary conditions are used. The trend extraction method is based on the idea that the smooth S_{J_0} is associated with the trend T_t and the details D_j are associated with the fluctuation ϵ_t [5]

$$\hat{T}_t = S_{J_0,t}; \qquad \hat{\epsilon}_t = \sum_{j=1}^{J_0} D_{j,t} \tag{9}$$

Table 2. Polynomial trend estimation of the minimum location of RR and RT series of 20 normal subjects (col. 1 and col. 5); standard errors of the the minimum location (col. 2 and col. 6); estimation of coefficient a_0 (col. 3 and col. 7); residual standard error (col. 4 and col. 8).

RR				*RT*			
953	7.7	0.001	10.8	1017	9.8	2e-04	4.7
1370	2.4	0.001	6.7	1469	5.9	2e-04	2.1
770	1.8	0.002	10.6	784	6.7	2e-04	4.5
558	3.4	0.001	9.6	584	7.6	2e-04	2.5
1220	2.9	8e-04	6.4	1306	3.1	3e-04	2.2
1956	2.8	3e-04	5.2	2014	5.1	3e-05	2.5
2093	1.3	6e-04	3.5	2234	2.1	2e-04	4.6
2018	2.6	1e-04	2.8	2172	4.1	2e-04	2.9
1230	1.9	5e-04	7.2	1265	2.9	1e-04	3.3
1355	3.9	6e-04	5.5	1380	6.3	2e-04	3.2
2147	4.2	4e-04	2.9	2208	6.3	1e-04	3.1
1534	3.3	3e-04	4	1691	6.1	4e-04	3.5
761	2.6	0.001	4.1	1064	3.3	2e-04	2.1
1221	3	0.001	6.6	1263	5.6	8e-05	4
1172	2.9	4e-04	10.9	1190	6	3e-04	3.9
1170	2.1	3e-04	7.3	1066	10.4	2e-04	2.9
1019	4.4	6e-04	8	1110	3.5	1e-04	3.6
1830	1.9	3e-04	4.6	1945	5.2	1e-04	2.8
1001	2.5	0.001	7.3	1095	3.8	2e-04	3.1
1418	2.9	7e-04	7.9	1425	10.7	4e-05	2.4

In our data all the series have length greater than $N = 2^{10} = 1024$, so the range of possible scale indices J_0 goes from 1 to 10. Obviously if $J_0 = 1, 2$, the trend S_{J_0} is not sufficiently smooth and the minimum location is biased by the fluctuation; if J_0 is large, say $J_0 \geq 7$, the trend S_{J_0} is conditioned by values that are far from the true location of the minimum. We have selected the intermediate scales $J_0 = 3, ..., 6$. These can be related to the running mean filter length by $2n + 1 = 2^{J_0} + 1, J_0 = 3, 4, 5, 6$. An example of the estimated trend is reported in fig. 4 for scales $J_0 = 3$ and $J_0 = 6$. The minimum locations for each of the 20 patients and each of the 4 scales are reported in table 3.

The estimated trend $\hat{T}_t$ is a bandpass version of the data series X_t with an approximate bandpass frequency of $[0, 2^{-(J_0+1)}]$ [5,17]. For $J_0 = 3, 4, 5, 6$ this means that we have applied respectively the cut off 0.062, 0.031, 0.015, 0.007 (in this approach the frequency range is $[0, 1/2]$).

4. Test on the RR-RT delay

We denote the minimum location of the trend T_t as

$$\tau = \text{argmin}_t \, T_t \tag{10}$$

Table 3. Wavelet estimation of the minimum locations of RR and RT series of 20 normal subjects, at four different scales. The last line contains means and standard deviations of minimum locations differences.

$J_0 = 3$		$J_0 = 4$		$J_0 = 5$		$J_0 = 6$	
RR	RT	RR	RT	RR	RT	RR	RT
968	876	966	1034	974	1024	971	1005
1359	1454	1366	1452	1377	1456	1379	1464
816	808	811	836	814	826	794	820
578	590	579	584	568	580	557	576
1209	1294	1216	1289	1225	1280	1231	1286
1962	2031	1988	2033	1978	2029	1980	2015
2091	2234	2086	2169	2083	2181	2093	2203
2027	2149	2034	2143	2023	2151	2016	2174
1292	1245	1284	1240	1270	1236	1254	1245
1392	1358	1385	1361	1373	1370	1360	1375
2092	2291	2070	2287	2085	2274	2106	2247
1565	1658	1564	1660	1569	1671	1553	1669
791	1016	785	1014	775	1023	762	1053
1243	1258	1234	1280	1224	1278	1210	1290
1218	1189	1216	1160	1219	1175	1206	1207
1159	1043	1166	1137	1176	1132	1175	1019
1043	1108	1036	1114	1027	1124	1034	1113
1892	1927	1883	1935	1871	1930	1855	1945
1032	1072	1033	1067	1022	1071	1002	1090
1442	1443	1435	1411	1420	1421	1436	1411
44 ± 89		53 ± 76		58 ± 74		62 ± 88	

and we denote τ^{RR}, τ^{RT} the minimum locations estimated from the trends of the RR and RT series. We consider to test the hypothesis

$$\tau^{RR} = \tau^{RT} \tag{11}$$

against the alternative $\tau^{RR} < \tau^{RT}$ and to estimate the RR-RT delay given by $\tau^{RT} - \tau^{RR}$.

We have used the standard paired t-test of comparison of the means. The sample of patients satisfies the standard assumptions for using this test: 1) the subjects in the study were randomly selected from the population of normal subjects; 2) we have checked using the Shapiro-Wilk test of normality that the measured values of RR-RT delay do not differ significantly from a normal sample.

Using data in Tab. 1 the hypothesis (11) is rejected with p-values less than 0.02 in the first running mean length and less than 0.002 in the others. The number of subjects in which the RR minimum does not precede the RT minimum are 7, 5,4,4 out of 20.

In Tab. 2 the columns 1 and 5 contain the estimate of the parameter c, i.e. the minimum location of RR and RT series. The mean delay is 74 beats with a standard deviation of 81, and the the hypothesis (11) is rejected with p=0.0006.

The same test for data in Tab. 3 rejects the hypothesis (11) with p-values smaller

than 0.05. The estimated delay, reported in the last row of the table 3, ranges from to 44 to 62 beats.

According to the results of the tests, our data clearly provide a rejection of the null hypothesis in favour of the existence of a RR-RT delay. As to the value of this delay some cautions are in order. In our study we have used data from 20 subjects. This number of subjects is not sufficient to quantify with precision a confidence interval for the delay. In addition this number is not sufficient to detect with a high power a small delay. More precisely we assume from our data that the standard deviation of the delay is 75 beats; a two tailed t-test with 20 subjects has a power 0.80 with a 0.05 level of significance to detect a delay of 50 beats (the power is 0.87 in a one-tailed test).

5. Residual analysis

At the maximal heart rate the level of fluctuation in RR series takes its minimum and becomes comparable with the time resolution (0.002 seconds) of the RR measure and this prevents us to analyze the RR residuals. We analyze the residuals ϵ_t obtained from the wavelet trend estimation of the RT series. We have considered the case $J_0 = 4$ so that the estimated residuals are defined as

$$\hat{\epsilon_t} = D_{1,t} + D_{2,t} + D_{3,t} + D_{4,t} \tag{12}$$

We first discuss the stationarity assumption. We have considered a window of 400 beats centered at the estimated minimum of each case; by visual inspection it turns out that about one half of the cases in our database show a stationary behavior. We have reported in fig. 5 two cases: a non stationary one (top) and a stationary one (bottom); both show symmetry around zero. The diagnostics of the stationary case is reported in fig. 6. The autocorrelation function is within the 0.95 confidence limits of a non correlated sequence (fig. 6, top). The Box-Pierce test for independence is non significant. The QQ plot for comparison to a normal distribution (fig. 6, bottom) shows a significant deviation from normality. The non parametric runs test for independence, however, does not reject the independence hypothesis. In summary in about one half of the cases the residuals satisfy the assumptions of the model (except normality). In the remaining cases the residuals show a non stationary behavior. We notice that the scale index J_0 plays a relevant role. Larger values, $J_0 > 4$, produce an increase of correlation in the residuals. This analysis of the residuals can be considered only a preliminary step for a mathematical model of the RT series. The fluctuation can bias both the value and the location of the minimum, but at our knowledge a quantification of this effect has not yet been investigated.

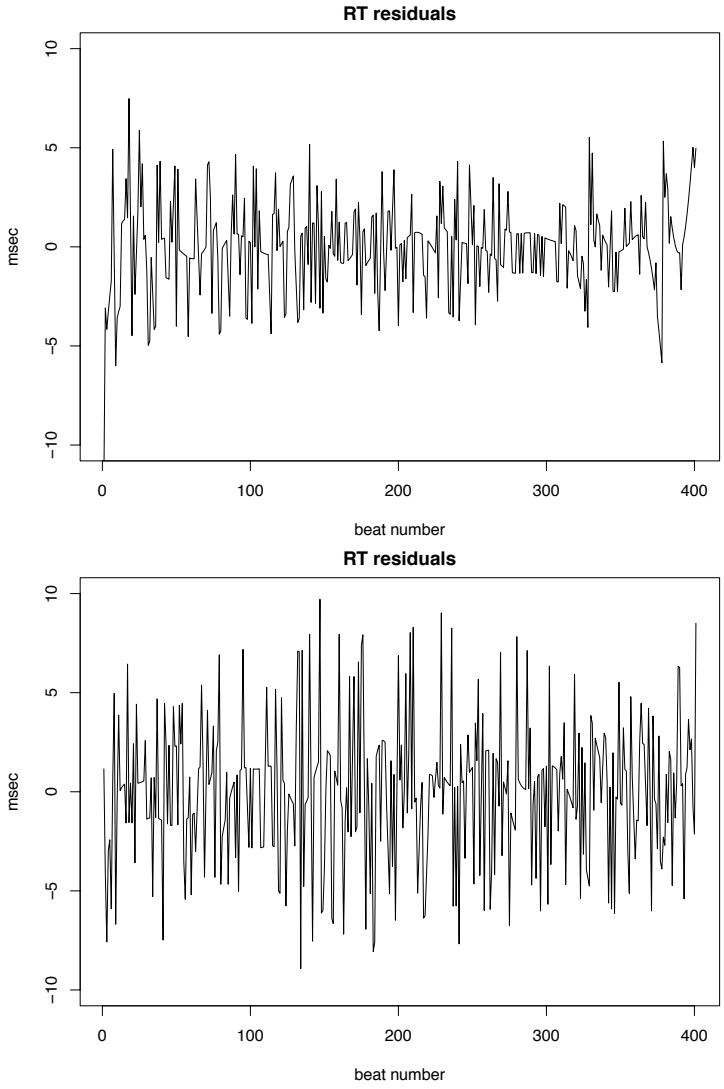

Fig. 5. RT residuals (in millisecond) versus beat number in a window of 400 beats centered around the minimum in two cases: a non stationary case (top) and a stationary one (bottom).

6. Conclusions

Accepted mathematical models of the non stationary RR and RT series are not available and consequently in our explorative analysis we have used different methods for trend extraction. We have focused on a very specific problem, i.e. to test for the difference in the minimum locations of the two series, as an index of the presence of the RR-RT delay. For each of the methods used, the standard paired t-test

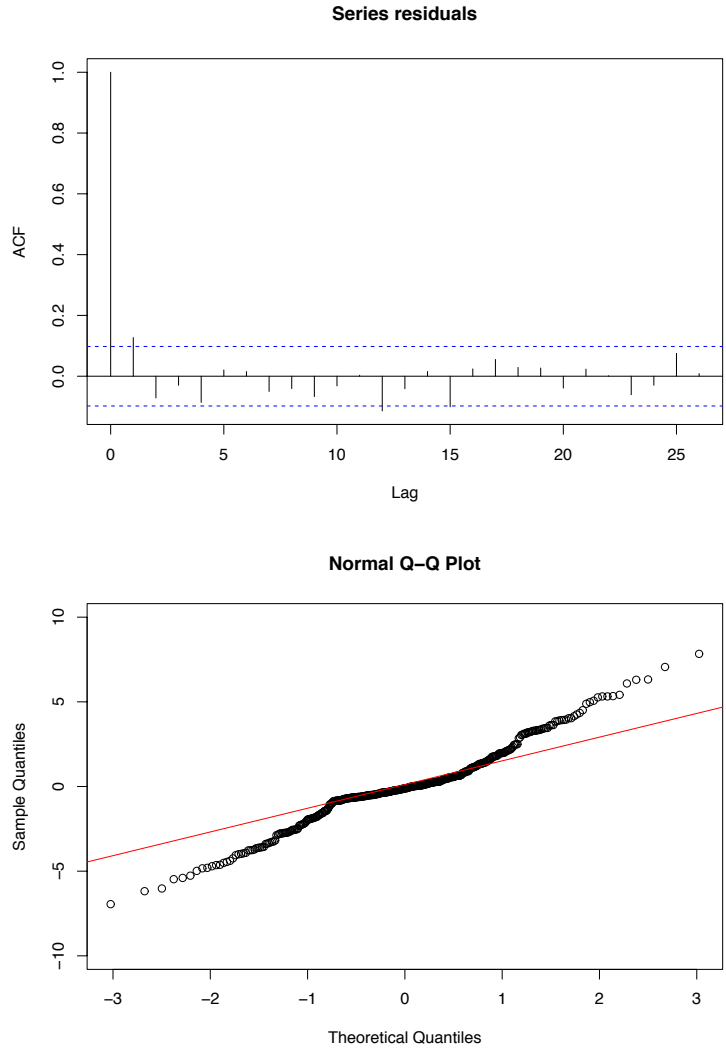

Fig. 6. Top: Autocorrelation function of RT residuals in a window of 400 beats in the stationary case; bottom: the QQ plot for comparison to normal distribution.

has rejected the hypothesis of equal minimum location, and provided evidence that the RT minimum follows the RR minimum. The existence of the RR-RT delay here obtained is in agreement to the result of previous investigations, but these were conducted in different conditions and with different methods [19, 20].

Previous models on the interaction between RR and RT were based on the assumption that the RR-RT delay exists in any individual. In our approach these

limitations are overcome, since we do not require the specification of a model of interaction. The analysis of tables from 1 to 3 suggests that in the majority of normal subjects the RR-RT delay exists, but that in some cases this could not be true. As it was explicitly remarked in [19] it is not possible to exclude a common factor driving both RR and RT so that a causal unidirectional model cannot explain entirely their variability. The large inter individual variability and the absence of the RR-RT delay in some individuals require further investigations, aimed to verify if these aspects reflect a physiological or a pathological condition. Our method could provide a new tool for this type of investigation, since it is not invasive and based on the a posteriori analysis of data from a routine laboratory test.

A possible explanation from the hemodynamic point of view for the RR-RT delay is the following. The sympathetic system has a twofold action: 1) it acts on the slope of the phase 4 of the transmembrane action potential of sinus node cells by increasing the frequency of discharge and so reducing the RR intervals; 2) it acts on phase 3 of the action potential by reducing the duration of RT (repolarization phase) mainly on the work cells. This allows a more rapid relaxation of myocardial fibers in protodiastole. Immediately after the acme the sharp reduction in the peak heart rate should be compensated by the persistence of the sympathetic activity on ventricular relaxation manifested by a persistence of RT in the minimum. From the electrophysiological point of view this physiological mechanism is able to protect the normal heart from life threatening arrhythmias that could be produced in its absence. Actually at high level of sympathetic activity at peak heart rate a sudden temporal prolongation of the repolarization, according to Bazett formula at rest, could trigger life threatening arrhythmias. More studies are needed on patients with cardiac disease to assess the presence or absence of this protective mechanism.

At the acme of the exercise the heart rate is very high; the mean RR duration of 20 cases is 378 milliseconds. We can roughly estimate the delay as 50 beats, so that the corresponding time delay is about 19 seconds. At the start of exercise the RR duration, computed as the mean of the first 100 beats, is much larger: its group mean is 667 milliseconds. In rest condition an estimate of the time delay obtained with the above argument should be 33 seconds.

Our estimated time delay (19 and 33 seconds) are remarkably smaller than the one found by [20], i.e. 2.36 minutes (corresponding to 150 beats). This difference can be in part explained since our mean includes negative values and in part since our estimate concerns normal subjects at maximal heart rate, while the other is from patients survivors of acute myocardial infarction at normal heart rate. Actually the response of RT to changes in RR interval could be faster at maximal heart rate than in normal conditions and normal subjects could have a faster adaptation than survivors of acute myocardial infarction.

Acknowledgments We thank Dr. Marisa Varrenti for helpful discussions during the revision phase of the manuscript.

References

[1] P.J. Brockwell and R.A. Davis. *Introduction to time series and forecasting*. Springer-Verlag, 2002.

[2] C. Cammarota and M. Curione. Analysis of extrema of heartbeat time series in exercise test. *Mathematical medicine and biology*, 25:87–97, 2008.

[3] C. Cammarota and M. Curione. Modeling trend and time-varying variance of heart beat rr intervals during stress test. *Fluctuations and Noise Letters*, 10:169–180, 2011.

[4] VS Chauhan, AD Krahn, BD Walker, GJ Klein, AC Skanes, and R Yee. Sex differences in qtc interval and qt dispersion: Dynamics during exercise and recovery in healthy subjects. *American Heart Journal*, 144(5):858 – 864, 2002.

[5] P. F. Craigmile, P. Guttorp, and D. B. Percival. Trend assessment in a long memory dependence model using the discrete wavelet transform. *Environmetrics*, 15(4):313–335, 2004.

[6] M. Curione, C. Cammarota, G. Cardarelli, S. Di Bona, T. Montesano, L. Travascio, M. Colandrea, M. Colotto, M. Ciancamerla, and G. Ronga. Qrs area monitoring during stress test: a novel index to separate normal to ischaemic patients? *Archives of medical science*, 4:51–56, 2008.

[7] P. Davey. How to correct the qt interval for the effects of heart rate in clinical studies. *Journal of Pharmacological and Toxicological Methods*, 48(1):3 – 9, 2002.

[8] L. Faes, A. Porta, and G. Nollo. Mutual nonlinear prediction as a tool to evaluate coupling strength and directionality in bivariate time series: Comparison among different strategies based on k nearest neighbors. *Phys. Rev. E*, 78(2):026201, Aug 2008.

[9] R. J. Gibbons and G. J. et al. Balady. Acc/aha guideline update for exercise testing: summary article. a report of the american college of cardiology/american heart association task force on practice guidelines committee on exercise testing. *J. Am. Coll. Cardiol.*, 40:1531 – 1540, 2002.

[10] PJ Kannankeril, PA Harris, KJ Norris, I Warsy, PD Smith, and DM Roden. Rate-independent qt shortening during exercise in healthy subjects: terminal repolarization does not shorten with exercise. *J Cardiovasc Electrophysiol.*, 19(12):1284 – 1288, 2008.

[11] R. Karasik, N. Sapir, Y. Ashkenazy, P. Ch. Ivanov, I. Dvir, P. Lavie, and S. Havlin. Correlation differences in heartbeat fluctuations during rest and exercise. *Phys. Rev. E*, 66(6):062902, Dec 2002.

[12] AD Krahn, GJ Klein, and R. Yee. Hysteresis of the rt interval with exercise: a new marker for the long-qt syndrome? *Circulation*, 96(5):1551 – 1556, 1997.

[13] C. P. Lau, A. R. Freedman, S. Fleming, M. Malik, A. J. Camm, and D. E. Ward. Hysteresis of the ventricular paced qt interval in response to abrupt changes in pacing rate. *Cardiovascular research*, 22(1):67–72, 1988.

[14] M.S. Lauer, C. E. Pothier, Y. B. Y. B. Chernyak, R. Brunken, M. Lieber, C. Apperson-Hansen, and J. M. Starobin. Exercise-induced qt/r-r-interval hysteresis as a predictor of myocardial ischemia. *Journal of Electrocardiology*, 39(3):315–323, 2006.

[15] J Leino, M Virtanen, M Kahonen, K Nikus, T Lehtimaki, T Tiit Koobi, R Lehtinen, V Turjanmaa, J Viik, and T Nieminen. Exercise-test-related heart rate variability and mortality: The finnish cardiovascular study. *International Journal of Cardiology*, 144(1):154 – 155, 2010.

[16] W. W. Melek, Z. Lu, A. Kapps, and W. D. Fraser. Comparison of trend detection algorithms in the analysis of physiological time-series data. *IEEE Transactions on Biomedical Engineering*, 52(4):639–651, 2005.

[17] D.B. Percival and A.T. Walden. *Wavelet methods for time series analysis*. Cambridge

University Press, 2000.

[18] V Pichot, J M Gaspoz, S Molliex, A Antoniadis, T Busso, F Roche, F Costes, L Quintin, J R Lacour, and J C Barthlmy. Wavelet transform to quantify heart rate variability and to assess its instantaneous changes. *Journal of Applied Physiology*, 86(3):1081–1091, 1999.

[19] A. Porta, G. Baselli, E. Caiani, A. Malliani, F. Lombardi, and S. Cerutti. Quantifying electrocardiogram rt-rr variability interactions. *Med Biol Eng Comput.*, 36(1):27 – 34, 1998.

[20] E. Pueyo, P. Smetana, P. Caminal, A. Bayes de Luna, M. Malik, and P. Laguna. Characterization of qt interval adaptation to rr interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction. *Biomedical Engineering, IEEE Transactions on*, 51(9):1511–1520, Sept. 2004.

[21] R Development Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2008. ISBN 3-900051-07-0.

[22] M. G. Rosenblum, L. Cimponeriu, A. Bezerianos, A. Patzak, and R. Mrowka. Identification of coupling direction: application to cardiorespiratory interaction. *Physical Review E - Statistical, Nonlinear and Soft Matter Physics*, 65(4 Pt 1):041909, 2002.

[23] K. Tanaka and A. R. Hargens. Wavelet packet transform for r-r interval variability. *Medical Engineering and Physics*, 26(4):313 – 319, 2004.

[24] N. Wessel, A. Suhrbier, M. Riedl, N. Marwan, H. Malberg, G. Bretthauer, T. Penzel, and J. Kurths. Detection of time-delayed interactions in biosignals using symbolic coupling traces. *EPL*, 87(1):1004p1 – 1004p5, 2009.