Trend extraction in functional data of R and T waves amplitudes of exercise electrocardiogram

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Abstract. The R and T waves amplitudes of the electrocardiogram recorded during the exercise test undergo strong modifications in response to stress. We analyze the time series of these amplitudes in a group of normal subjects in the framework of functional data, performing reduction of dimensionality, smoothing and principal component analysis. These methods show that the R and T amplitudes have opposite responses to stress, consisting respectively in a bump and a dip at the early recovery stage. We test these features computing a confidence band for the trend of the population mean and analyzing the zero crossing of its derivative. Our findings support the existence of a relationship between R and T wave amplitudes and respectively diastolic and systolic ventricular volumes.

Keywords: ECG; R wave; T wave; exercise test; time series; trend; functional data; extrema; maxima; minima.

1. Introduction

The electrocardiogram (ECG) recorded during the exercise test is used in clinical practice to evaluate the presence of myocardial ischaemia Gibbons and Balady [2002]. During the test the patient on a bicycle ergometer is subjected to a workload increasing in time (stress phase). When the heart rate reaches its maximum (acme), the exercise is stopped and gradually the heart rate recovers its basic value (recovery phase). The R and T waves of the ECG (fig. 1) occur respectively at the end of the ventricular diastolic phase (telediastole) and at the end of the systolic phase (telesystole), which are the times of maximum and minimum ventricular filling.

Great attention was devoted in clinics to the modifications of the QRS complex (fig. 1) during exercise. The QRS amplitude was found to show opposite directional changes in different studies Kligfield and Lauer [2006]. These non univocal findings are due mainly to two factors: the great inter individual variability of the response to exercise in normal subjects and the large fluctuations in amplitude of the ECG waves that occur at the time scale of few beats. Observations localized in time as the ones typical of clinical research revealed not sufficient to extract significant directional changes during the exercise. ECG and vectorcardiographic parameters related to R and T waves during exercise have been recently investigated Lipponen et al. [2013], Kania et al. [2015], Bortolan et al. [2015]. In different conditions concomitant variations of R and T waves were observed and their relationship to the changes in

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ventricular cavity size were conjectured Feldman et al. [1985]. These variations and their relationships to changes in ventricular volume during exercise have been not sufficiently investigated, to the best of our knowledge.

The RR interval, defined as the time interval between two consecutive R peaks in the ECG, is inversely related to the heart rate. The sequence of RR intervals during exercise is characterized by a V-shaped profile, in which the minimum corresponds to the acme (see the RR series of a group of normal subjects in fig. 2, top). The series of RR and of RT intervals, that is characterized by the same profile, can be investigated using the standard model of decomposition of a series into trend plus noise using non parametric methods Wasserman [2006], Ruppert et al. [2009]. The trend extraction allows to reveal directional changes in time or to detect maxima and minima in RR and RT series Cammarota and Curione [2008, 2011, 2012]. A related approach aimed to assess the significance of extrema in one series of observations is the `R` package `SiZer` (Significance of Zero crossings of derivatives) Sonderegger [2011], Chaudhuri and Marron [1997].

These methods however are restricted to the analysis of individual series. Modern datasets of medical data are often in the form of longitudinal data: one or more indices are measured repeatedly in time in a group of subjects and one can assume independence among individuals Verbeke et al. [2014]. When the time resolution is sufficiently high so that the data reveal an underlying curve, this type of dataset is known as 'functional data', and it has recently obtained much attention in statistical literature Ramsay and Silverman [2006], Ferraty and Vieu [2006]. In medical datasets the population mean of functional observations reflects a collective behavior of an observable as a function of time. A typical problem is the trend extraction of the population mean aimed to detect the relevant features and to test their significance. Theoretical investigation has been devoted to assess if the population mean is non constant in time, and to provide a related test of significance. This test is based on the estimate of a confidence band of the population mean Cao et al. [2012], Degras [2011], Song et al. [2014], Bunea et al. [2011], Azais et al. [2010]. Several software tools have been introduced to analyze functional data: one of these is the `R` R Development Core Team [2008] package `fda` Ramsay et al. [2012]. Functional data methods revealed recently useful in the analysis of the ECG Ieva and Paganoni [2013].

In the present paper we analyze the functional data of RR intervals and of R and T waves amplitudes measured during the exercise test of a group of normal subjects (fig. 2). The R wave amplitude is strongly linked to the area of QRS complex that was previously investigated for both normal and ischaemic subjects during exercise Curione et al. [2008]. It was observed that the population mean time profile during the early recovery phase, i.e. immediately after the acme, shows a reduction in QRS area values. Our aim in the present work is twofold: 1) to test the significance of the minimum in R amplitude series at early recovery phase, previously observed Curione et al. [2008]; 2) to investigate the concomitant presence of a maximum in T amplitude series and to assess its significance.

2. Model and methods

2.1. **Electrocardiogram measurement and analysis.** In multistage Bruce protocol Gibbons and Balady [2002] the patient on a bicycle ergometer is subjected to a

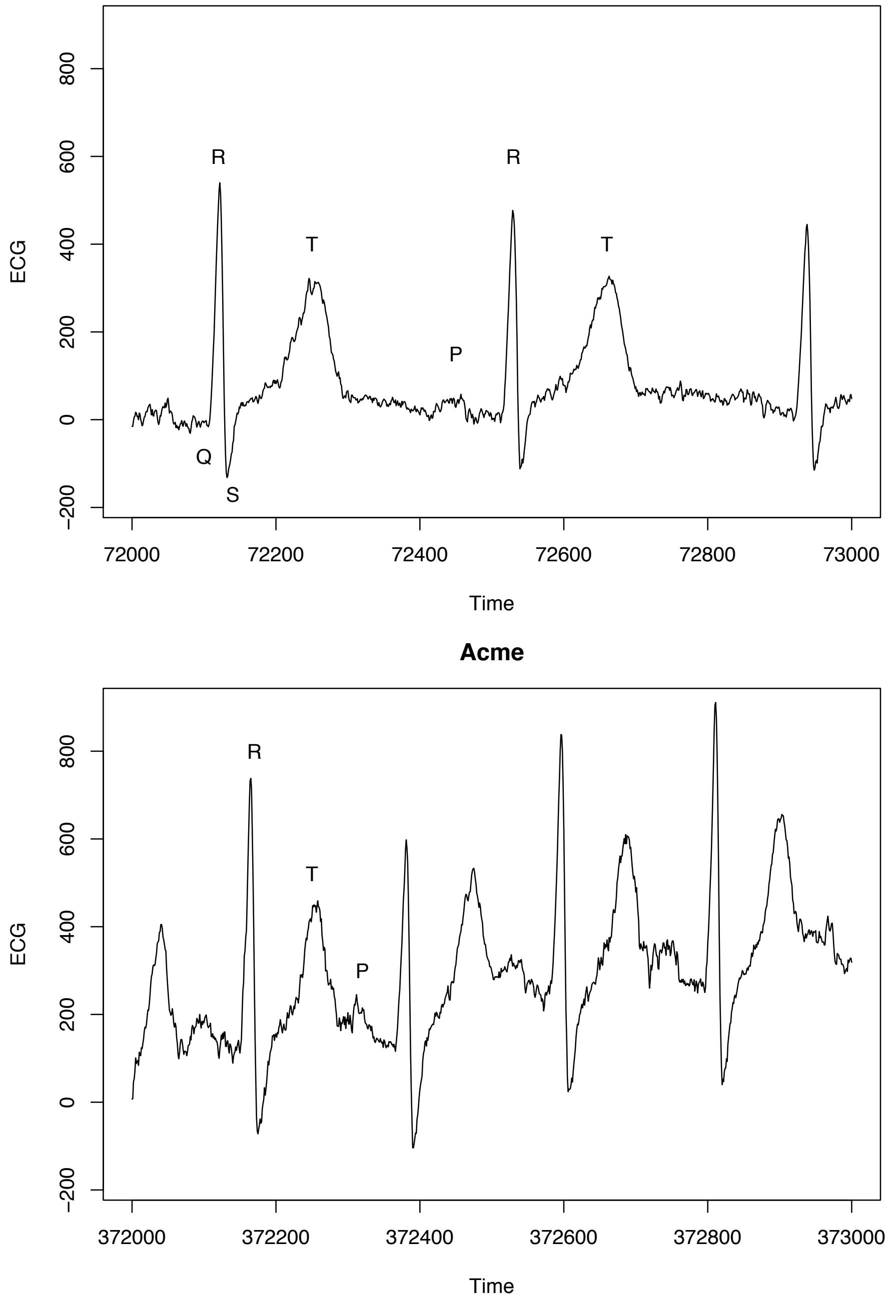

FIGURE 1. Two-seconds recording of ECG during exercise test (raw data from the lead V5). Top: The ECG signal at the start of the test (rest condition) with the R peak and the apex of T wave. Bottom: the signal at the acme, when the RR interval takes its minimum; T wave offset overlaps with the subsequent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

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 a 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.

For the RR extraction the precordial lead V5 was chosen, because it is less influenced by motion artifacts (fig.1). The R peak detection was performed using a derivative-threshold algorithm and the onset and offset of the QRS complex were identified. For each QRS complex the R amplitude was defined as the maximum minus the minimum of the signal in the window between the onset and the offset of the complex. The local value of the baseline was defined as the mean of the two values of the signal in the onset and in the offset of the QRS. The T amplitude was detected as the maximum of the signal computed in a window subsequent to each R peak between 15% and 50% of the preceding RR interval and referred to the local baseline; no negative T waves were present in our recordings. Abnormal or undetected beats were less than 1% of the total beats for each subject. RR intervals falling outside the normal range due to undetected beats were replaced with the median computed over blocks of 30 adjacent beats. The algorithm discarded the R and T amplitudes related to undetected QRS complex. Analysis of raw data, R and T peak detection and subsequent computations were performed using the free statistical software `R` R Development Core Team [2008].

2.2. **Data registration and normalization.** We denote the data series of the i th subject as

$$X_i(t), \quad i = 1, ..., n; \qquad t = 1, ..., m_i \tag{1}$$

where t is the beat number index and n is the number of individuals. The lengths m_i range from 1500 to 3000 beats. During the test the duration of the RR interval, inversely related to the instantaneous heart rate, shows strong modifications: at maximal heart rate (acme) the RR interval is about one half than the basal value. Changes of amplitude of the R and T waves occur prevalently after the acme, but with variable delays (phase variation). Data registration is an operation required in order to align prominent features. We use the landmark registration based on the fact that each RR series has a global minimum, occurring at beat number, say t_i^*, the acme. Data registration of R and T series is performed putting the time of this common feature into a common value. This is accomplished extracting a window of $m = 1200$ beats centered at t_i^* in each series, in such a way that the acme occurs at beat number 600. In the sequel we restrict the analysis to this window. Fig. 2 provides a representation of the data in this window. We assume as a model for the data

$$X_i(t) = U_i\ (\mu(t) + Z_i(t)) \tag{2}$$

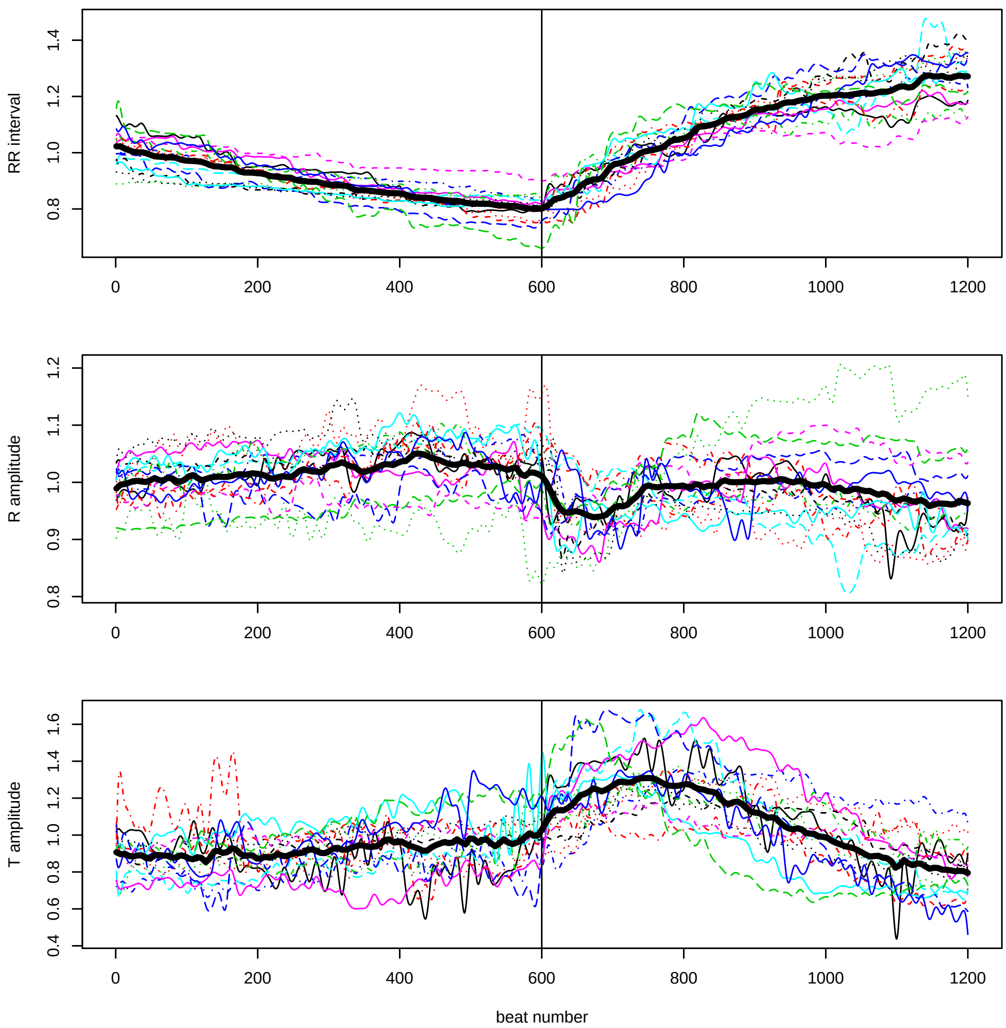

FIGURE 2. Time-mean normalized and aligned series of a group of 16 normal subjects and their population mean (thick black line) of RR interval (top), R amplitude (centre) and T amplitude (bottom) during the exercise test. The vertical line denotes the acme. The series are restricted to a window of 1200 beats centered at the acme. Adimensional units on vertical axis. Color on line.

where the population mean $\mu(t)$ is a deterministic function of time and $Z_i(t)$ are independent r.v. with zero mean and $\mathbb{V}ar Z_i(t) = \sigma_i(t)^2$, representing error measurement and random individual deviations from the population mean; the factor U_i accounts for the individual amplitude of the ECG signal, that affects proportionally the amplitudes of the R and T waves. This factor plays the same role of an individual additive effect in longitudinal data models. Since we are interested in relative variation of the variables during time, we normalize each series dividing by its temporal mean, and define the normalized data as

$$Y_i(t) = \frac{X_i(t)}{\frac{1}{m}\sum_{t=1}^{m} X_i(t)} \tag{3}$$

Denoting

$$D_i = \frac{1}{m}\sum_{t=1}^{m} X_i(t) \tag{4}$$

and

$$\overline{\mu} = \frac{1}{m}\sum_{t=1}^{m} \mu(t)$$

one has

$$\mathbb{E}\ D_i = U_i\ \overline{\mu}\ ; \quad \mathbb{V}ar\ D_i = \frac{1}{m}U_i^2\sigma_i^2$$

where $\sigma_i^2 = \frac{1}{m}\sum_t \sigma_i(t)^2$. Since in our dataset m is large the coefficient of variation of D_i

$$\frac{\sigma_i}{\sqrt{m}\ \overline{\mu}}$$

is small, so one can approximate the r.v. D_i with its expected value $U_i\overline{\mu}$. Hence the normalized data can be modeled as

$$Y_i(t) = (\mu(t) + Z_i(t))/\overline{\mu} \tag{5}$$

In the normalized data the population mean $\mu(t)/\overline{\mu})$ has a time mean equal to 1, as shown in the three panels of fig. 2. In the model rewritten as

$$Y_i(t) = \tilde{\mu}(t) + \tilde{Z}_i(t) \tag{6}$$

our aim is to detect maxima and minima of $\tilde{\mu}(t)$.

2.3. **Reduction of dimensionality and smoothing.** The basic operation for functional data is the reduction of dimensionality, that in our case is given by $m = 1200$ observations. This can be done choosing an orthonormal set that spans a suitable functions subspace and projecting on this subspace. We use B-splines made with cubic polynomials Ruppert et al. [2009]

$$\psi_k(t), \quad k = 1, ..., K$$

with K of the order of 100. Since these are smooth functions, the reduction of dimensionality produces a smoothing of the series. Each function $Y_i(t)$ can be replaced by its smoothed version $S_i(t)$, according to

$$S_i(t) = \sum_{k=1}^{K} c_{i,k}\ \psi_k(t) \tag{7}$$

where the $c_{i,k}$ are suitable coefficients. The smoothed population mean $\overline{S}(t)$ is defined as

$$\overline{S}(t) = \frac{1}{n}\sum_{i=1}^{n} S_i(t) \tag{8}$$

2.4. **Principal Component Analysis.** The Principal Component Analysis (PCA) in functional datasets is a method for reduction of dimensionality and analysis of variance, that uses a basis of principal components, the eigenfunctions of the covariance matrix. Obviously the smoothed version of the data is used. Using the first two components $\phi_1(t)$, $\phi_2(t)$ of this basis, denoted PC1 and PC2, for each individual labeled by i one has the approximation

$$S_i(t) \simeq \overline{S}(t) + c_{i,1}\phi_1(t) + c_{i,2}\phi_2(t) \tag{9}$$

The components PC1 and PC2 of the group and the individual loadings $(c_{i,1}, c_{i,2})$ are represented in fig. 3.

2.5. **Confidence band of the population mean.** An obvious estimator of $\tilde{\mu}(t)$ is the smoothed population mean $\overline{S}(t)$. The construction of a confidence band for the population mean has been recently investigated Cao et al. [2012], Degras [2011], and we apply to our case the results reported in literature on the pointwise confidence band in the normal approximation. An estimator of the variance of $\tilde{Z}(t)$ is

$$\hat{\sigma}(t)^2 = \frac{1}{n-1}\sum_{i=1}^{n}(S_i(t) - \overline{S}(t))^2 \tag{10}$$

Then the $1-\alpha$ level confidence band is

$$\overline{S}(t) \pm \hat{\sigma}(t)\ z_{1-\alpha/2}\ n^{-1/2} \tag{11}$$

where $z_{1-\alpha/2}$ is the standard normal quantile.

2.6. **Feature extraction.** In the model eq. 6 of the raw data series we consider the population mean, defined by

$$\overline{Y}(t) = \frac{1}{n}\sum_{i=1}^{n} Y_i(t) \tag{12}$$

that can be rewritten as

$$\overline{Y}(t) = \tilde{\mu}(t) + W(t) \tag{13}$$

where the error term is now

$$W(t) = \frac{1}{n}\sum_{i=1}^{n} \tilde{Z}_i(t) \tag{14}$$

The estimate of $\tilde{\mu}(t)$ can now be considered as a problem of trend extraction from $\overline{Y}(t)$. This is a non smooth function presenting several maxima and minima, and our aim is to extract the significant ones (feature extraction). The same problem has been considered in different applications (see for instance Song et al. [2006]) and it consists essentially in constructing a confidence band for $\tilde{\mu}(t)$ and for its derivative. The `R` package `SiZer` (Significance of zero crossings of derivatives) Sonderegger [2011], Chaudhuri and Marron [1997] has been developed for the exploration of structures in curves. This package uses a locally weighted polynomial regression centered at each point $t_j,\ j = 1, ..., k$ of a grid, a suitable subset of the time values; a kernel gives a weight to each point; for each grid point the estimated parameters provide the local trend and slope. The weight has the form

$$w_j(t) = \frac{K((t-t_j)/h)}{\sum_t K((t-t_j)/h)} \tag{15}$$

where K is a symmetric function concentrated near zero, for instance a Gaussian, and h is the bandwidth. We use a second order polynomial

$$P_j(t) = \beta_0^{(j)} + \beta_1^{(j)}(t-t_j) + \beta_2^{(j)}(t-t_j)^2 \tag{16}$$

and the parameters $\beta_0^{(j)}, \beta_1^{(j)}, \beta_2^{(j)}$ are estimated minimizing for any j the quantity

$$\sum_t (\overline{Y}(t) - P_j(t))^2 w_j(t) \tag{17}$$

The value of h acts as a smoothing parameter. The coefficients of zeroth order $\beta_0^{(j)}, j = 1, ..., k$ are an estimator of the level; similarly the coefficients of first order $\beta_1^{(j)}$ are an estimator of the derivative.

3. Results

We have analyzed 16 normal subjects (aged 45 ±15 years) who underwent the test performed according to the Bruce protocol in a preceding study of our group Curione et al. [2008] to which we refer for clinical details. The RR intervals at rest range from 400 to 800 ms; the R amplitudes range from 1 to 3 mV and the T amplitudes range from 0.2 to 1 mV. The series are subjected to data registration and normalization. The smoothing is performed using a splines basis constructed over a grid of 135 knots. The resulting RR, R and T series are plotted in fig. 2 for the 16 individuals (color on line).

The principal component analysis for our dataset is extremely effective, since the explained variance with the first two components PC1 and PC2 of R wave is 99% and of T wave is 94%. The correlation between $c_{i,1}$ and $c_{i,2}$ of R and of T are non significantly different from zero as expected (fig.3, first row). Both PC1 components reflect the mean trend near the acme (beat number 600): a local minimum for R and a maximum for T. Both PC2 components intersect the zero line at acme, reflecting a contrast effect between exercise and recovery (fig. 3, second row).

As already known each individual RR series shows a well defined V shaped profile; this profile is non symmetric, with the stress phase (before the acme) and the recovery phase (after the acme) having different slopes. The R and T individual series on the contrary show several local extrema, most of which should be not significant, reflecting individual random responses to exercise (fig. 2). The inspection of the population mean (the thick line superimposed on the plots of R and T in fig. 2), shows the simultaneous occurrence of a dip in R and of a bump in T series during the early recovery phase. We have conjectured that this evolution, not previously reported, characterizes the normal response to exercise. In order to assess the significance of these features we test the hypothesis that the population means of R and T series are constant in time. In other words the null hypothesis is that the data do not contain any information different from noise. In fig. 4 we represent the confidence band with $\alpha = 0.05$ and $z_{1-\alpha/2} = 1.96$, computed using eq. 11 and the constant straight line of height equal to the time mean. In both R and T series just after the acme the

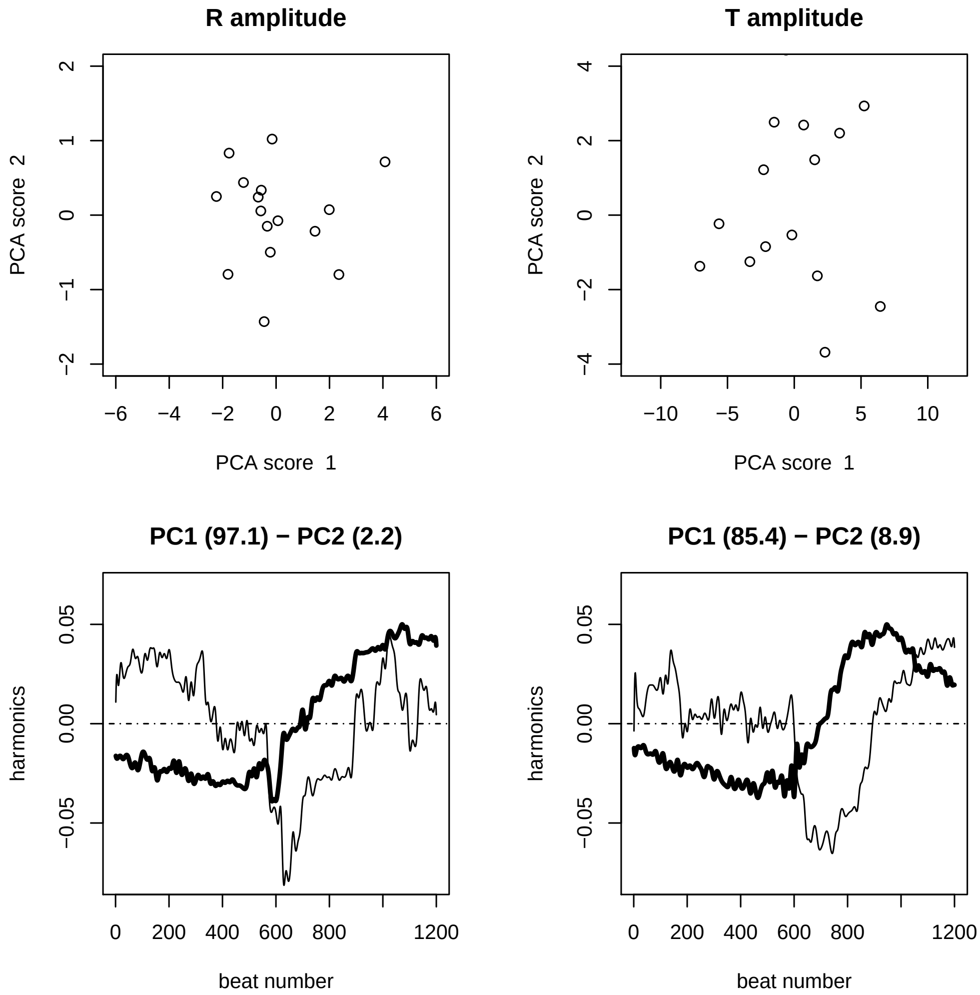

FIGURE 3. First row: R and T loadings on the two first principal components (PC1 and PC2); second row: normalized PC1 (thick line) and PC2 of R and T amplitudes (after mean subtraction).

confidence band does not include the constant line, so we conclude that respectively the dip in R data and the bump in T data are significant.

A second approach is based on the analysis of the residual variability in the raw population mean, obtained using the eq. 13. For the localization of a local extremum in a series we adopt the method based on the zero line crossing of the derivative: an extremum is significant if the derivative is different from zero and has opposite signs before and after the zero crossing. If the zero level line is contained in the confidence band of the derivative, local maxima and minima are not significant. The SiZer package provides a confidence band for the population mean $\tilde{\mu}(t)$ and for its derivative, according to the method described in the previous section. As expected the two main features of the population mean of R and T series, the dip of R and the bump of T, occurring just after the acme, are significant (fig. 5).

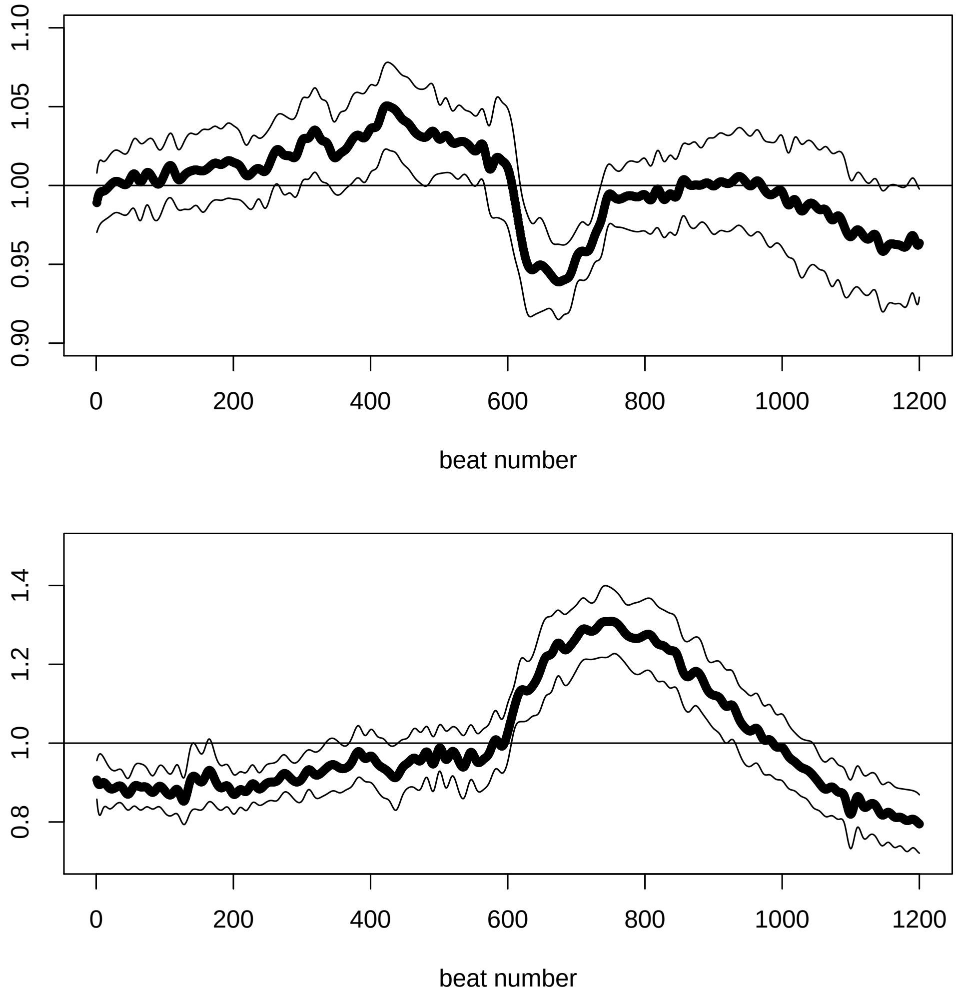

FIGURE 4. Confidence band of level 95% of the population mean of R (top) and T (bottom) amplitude (adimensional units)

4. DISCUSSION

Two main sources of variability are present in the exercise ECG data. The first one is the inter individual variability, which reflects the different individual responses to the stimulation during the test. The second source of variability is due to the random fluctuations in time that are present in each signal, mainly due to the error measurement. Both these effects produce the peaks and valleys observed in each individual series of R and T amplitudes.

We have performed a test on the trend of the population mean of R and T amplitudes in the framework of functional data. This test based on the confidence band of the population mean has revealed that the T amplitude has a clear response to stress, consisting in a bump after the acme. To the best of our knowledge this result is new. This test has also provided evidence of a concomitant dip in the R amplitude, that was described in Curione et al. [2008]. The second test conducted using the feature

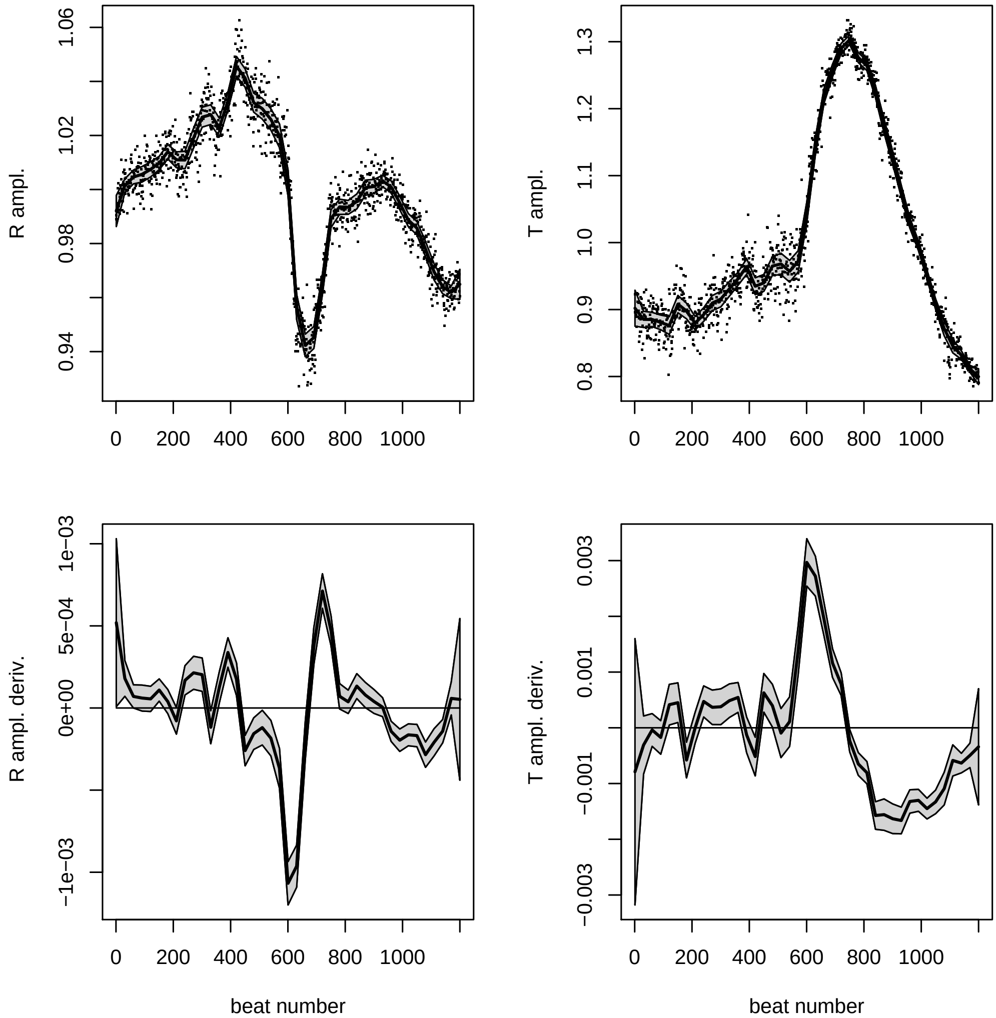

FIGURE 5. First row: R and T population mean amplitude profile (adimensional units) with their 95 % confidence band (gray), and observed values (dots); Second row: estimated derivatives and confidence band. The bandwidth is $h = 20$.

extraction of the raw population mean confirmed these results, revealing that both the derivatives of R and T amplitude have a significant zero crossing.

A comparison of the two normalized population mean profiles (fig. 4) shows that the amplitude of the maxima of the T series is greater than the corresponding minimum of the R series. These different findings in R and T behavior could reflect a weaker response of the R wave to exercise or different individual timings of the dip in R amplitude with respect to the acme. Our dataset is characterized by a small number $n = 16$ of individuals, and a large numbers $m = 1200$ of observations. Unfortunately theoretical results such as Cao et al. [2012], Degras [2011] concern asymptotic behavior for $m \to \infty$, $n \to \infty$ and finite sample size approximation results are not available. Our results should be confirmed by a larger sample of individuals. An interesting related open problem is to provide confidence intervals of the time location and of the amplitude of the extrema, as related to measurement noise and inter individual variability. The normalization of the data series has the effect of reducing the inter individual variability (each series has time mean equal to 1), allowing to focus on the time variability. An open problem is to investigate the population mean of non normalized data, for which the large inter individual variability could mask some of the observed effects.

The principal component analysis has revealed that a very large proportion of variance is explained by the first two components. This allows a simple bidimensional representation of the individuals, that could be of clinical use, for instance in finding abnormal behavior and in clustering.

Our results suggest that the population profiles of R and T waves undergo significant opposite directional changes just after the acme as a normal response to exercise. They integrate the previous ones obtained on the R waveCurione et al. [2008], thus confirming the relationship between electrocardiographic and hemodynamic variables in normals. This relationship was observed in some clinical experimental conditions in which endoventricular volume progressively changes, such as during haemodialysis Curione et al. [2013].

These findings have an interesting physiological interpretation and possible clinical applications. In the normal subjects here examined the mean time profile of R and T during increase in heart rate is stable and this finding could be referred to normal diastolic ventricular function. Opposite trends in R and T wave amplitude after the acme seem to show telediastolic and telesystolic volume changes respectively, as they present a specular behavior according to the Frank-Starling law. The mechanism underlying to this phenomenon is complex and still debated, but the role played by changes in intraventricular volume seems to be the most reliable. Increasing telediastolic volume leads to an increase in electrical resistivity due to higher number of red cells in the left ventricular chamber. This mechanism could play a role both in R and in T wave amplitude changes, representing respectively telediastolic and telesystolic volume changes. The R and T amplitudes profiles could have a clinical application to ischaemic patients identifying abnormalities in haemodynamic performance during the exercise test Curione et al. [2008].

The present work has several limitations of various types. The detection of QRS and the measure of R and T amplitudes are influenced by the noise in the signal, in particular by the electromyographic noise. We have not tested the robustness of our findings with respect to the addiction of noise to the signal. The performance of the method should be tested also with respect to different detection algorithms. During the exercise the T wave shape undergoes strong modifications, the main of which is the overlapping of T wave offset with the subsequent P wave onset. This prevents us from considering the energy area of the T wave that similarly to the one of the QRS complex has been usually adopted. Our physiological interpretation of the extrema in R and T trends should be confirmed by a direct measure of venous return and ventricular volume during exercise. The respiratory-related oscillations of the cardiac axis and of the electrical impedance have been not considered. The importance of these phenomena on the shape of T wave was discussed in Lombardi et al. [1996], Porta et al. [1998]. However, these effects occur on a scale of a few seconds, while the observed extrema occur on a larger time scale.

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6. Conflict of interest

The Authors declare that there is no conflict of interest.

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