A Spatio-Temporal Study of Ischemia and the Time-Frequency Coupling Variations between the ST Amplitude, Heart Rate and Dominant Angle

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Abstract

An analysis of the Long Term ST Database (LTSTDB) was conducted to quantify the spatio-temporal dynamics of ischemic and non-ischemic episodes. For all 86 recordings the ischemic episode length is decribed by a log-normal distribution and the non-ischemic episode length by a generalized extreme value distribution. For the 15 recordings that possess orthogonal (EASI) leads sets we derived the 12 standard leads and analyzed the spatial time course (from the j-point to j+120 ms) of each episode over time to identify dominant trends. Although the magnitude of the ischemic episodes did not reveal any inter-subject trend (except for generally exhibiting Brownian-like motion), there appeared to be strong correlations with the heart rate (HR). Wavelet cross-spectral coupling with significance testing was then applied to the ST-amplitude and HR evolution over the course of each episode. In all subjects significant cross-spectral correlations were found at very low frequencies (<0.04 Hz), as well as at respiration and baroreflex frequencies. This may indicate that the ischemic episodes are modulated by blood pressure and activity or HR-related phenomena and that all episodes in the LTSTDB may be of a 'mixed' type at some point in their duration. The dominant angle also showed significant correlation (p<0.01) with the ST amplitude and HR changes at similar frequencies to those described above. All three protocols used to define ischemia in the LTSTDB gave similar results.

1. Introduction

Modelling the short- and long-term spatial and temporal changes in the ECG during ischemia provides a mechanism for baseline testing of relevant signal processing algorithms. Our aim in this work was to provide a description of such changes in order to provide information to build an accurate simulation of the ECG during ischemia.

2. Methods

2.1. Data

The data used in this study were taken from the Long-Term ST Database (LTSTDB) [1] available from PhysioNet which contains 21-24 hour multi-channel ECG recordings and annotated ischemic and non-ishemic ST changes. An ischemic episode was defined to start when the ST deviation exceeded a lower threshold, $V_{lower} = 50\mu V$. Next, the deviation was required to reach or exceed an upper threshold, V_{upper}, for at least a continuous interval of T_{min} seconds. Finally, the episode ended when the deviation dropped to less than $V_{lower} = 50\mu V$ in the following $T_{sep} = 30$ s. The values of (V_{upper}, T_{min}) were (75 μV, 30 s), (100 μV, 30 s) and (100 μV, 60 s) defined as protocol STA, STB and STC respectively.

All analysis was performed in the vectorcardiogram (VCG) space. The LTSTDB contains 15 recordings (s30691 through s30801) which used the EASI lead system [2]. The standard 12-lead and vectorcardiogram (VCG) lead systems can be derived directly from these leads by using a variety of under- or over-complete linear transforms. We chose the transformation coefficients corresponding to Mason-Likar leads because they were adjusted to give the best ST-segment fit [2]. The matrix of coefficients T^{ML} corresponding to the transformation from the three lead EASI configuration,E^{ML}, to the standard 12-lead ECG (I, II, II, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6), E^S, is given by Feild *et al.* [2] such that $E^S = T^{ML}E^{ML}$. Similarly they give the transformation from the EASI configuration to the vectorcardiogram (X, Y, Z) configuration, V, the matrix T^V such that $V = T^V E^{ML}$.

2.2. Temporal analysis of the episodes

The lengths of each ischemic and non-ischemic episode for all 86 patients in the LTSTDB were calculated using all available leads. An episode was taken to start if any lead satisfied the criteria for the relevant protocol and was taken to end when all leads ceased to satisfy the same pro-

tocol. The distributions of the lengths of the episodes were tested against five standard distributions; the exponential (f^e), the lognormal (f^{ln}), the inverse Gaussian (f^{iG}), the loglogistic (f^{ll}) and the generealized extreme value (f^{gev}) as follows:

$f^e(\lambda;\eta) = \eta e^{-\eta\lambda}, \lambda \geq 0$

$f^{ln}(\lambda;\mu,\sigma_n) = (\lambda\sigma_n\sqrt{2\pi})^{-1}e^{-\frac{(\ln\lambda-\mu)^2}{2\sigma_n^2}}, \lambda \geq 0$

$f^{iG}(\lambda;\mu,\sigma) = \left(\frac{\sigma}{2\pi\lambda^3}\right)^{1/2} e^{\frac{-\sigma(\lambda-\mu)^2}{2\mu^2\lambda}}, \lambda > 0$

$f^{ll}(\lambda;\mu_s,\xi) = \frac{(\xi/\mu_s)(\lambda/\mu_s)^{(\xi-1)}}{(1+(\lambda/\mu_s)^\xi)^2}, \lambda > 0$

$f^{gev}(\lambda;\mu_l,\mu_s,\xi) = \frac{\mu_s^{-1}e^{-\left[1+\xi\left(\frac{\lambda-\mu_l}{\mu_s}\right)\right]^{-1/\xi}}}{\left[1+\xi\left(\frac{\lambda-\mu_l}{\mu_s}\right)\right]^{1+(1/\xi)}}, \frac{\xi(\lambda-\mu_l)}{\mu_s} > -1$

For the exponential distribution, η is the rate parameter of the distribution; for the lognormal distribution, μ is the mean and σ_n the standard deviation of the natural logarithm of the variable; for the inverse Gaussian, μ is the mean and σ the standard deviation; for the loglogistic, μ_s is the scale parameter and ξ the shape parameter; and, for the generalized extreme value, μ_l is the location parameter, μ_s the scale parameter, ξ the shape parameter.

Both ischemic and non-ischemic episodes were segmented into 24 bins, according to the hour of the day in which the episode started. The 2-sample Kolmogorov-Smirnov test was used to test for significant differences in ST changes between each hour, and between ischemic and non-ischemic episodes. Tests were then performed to discover if the length of episodes was related to HR or heart rate variability (HRV), including the standard deviation of the HR and the LF/HF-ratio.

2.3. Spatial analysis of the episodes

Since we have observed that ischemic episodes can manifest more strongly on one lead, yet this lead can change over the course of an episode (or between episodes), we defined the notion of a dominant or 'prefered' ischemic direction (PID). The PID corresponds to the angle at which the largest amplitude of the ST segment in the VCG space, $|V| = (V_x^2 + V_y^2 + V_z^2)^{1/2}$ of the dipole $\hat{V}$ at the $t = j + 80(60)$ point. To quantify the movement of the PID, the VCG was transformed from cartesian to spherical coordinates using $\theta = \arctan V_y/V_x$, $\phi = \arctan V_z(V_x^2 + V_y^2)^{-1/2}$, where $|V|$ is the radius, and the angles ϕ and θ are the *elevation* and *azimuth*, respectively. The elevation, ϕ, is measured from the x-y plane and ranges from -90 degrees to 90 degrees. The azimuth, θ, is the angular displacement measured from the positive x-axis (pointing out the front of the torso) and ranges from -180 degrees to 180 degrees.

2.4. Time-frequency correlation

To assess dependencies between the non-stationary signals dominant angle (θ, ϕ), ST amplitude ($|V|$) and HR, we applied cross-spectral wavelet coherence analysis [3]. The aim is to estimate transient associations between two signals along time and frequency (period or scale). To quantify the cross-correlation between two time-series in time-frequency space, it is necessary to compute the cross-wavelet transform and the wavelet coherence. The cross wavelet transform of two time series $x(t)$ and $y(t)$ is given by $W_{x,y}(a,\tau) = W_x,(a,\tau)W_y^*(a,\tau)$ where $W(a,\tau)$ is the wavelet transform, * denotes the complex conjugate, τ is the translation (time shift) factor and a is the dilation (scale factor). (We chose the Morelet wavelet for this analysis.) The cross-wavelet power defined as $|W_{x,y}(a,\tau)|$ measures the common power of the two time series. The wavelet coherency is defined as [4]:

$$C_{x,y}^2(a,\tau) = \frac{|\langle\frac{1}{s}W_{x,y}(a,\tau)\rangle|^2}{\langle\frac{1}{s}|W_{x,x}(a,\tau)|^2\rangle\langle\frac{1}{s}|W_{y,y}(a,\tau)|^2\rangle} \quad (1)$$

where $\langle\rangle$ represents a smoothing operator achieved by a convolution in time and scale such that:

$$\langle W(a,\tau)\rangle = \left[\left(c_1 W(a,\tau)\otimes e^{\frac{-\tau^2}{2s^2}}\right)_\tau \otimes c_2\Pi(\alpha s)\right]_s$$

where c_1 and c_2 are normalization constants, Π is the rectangle function and $\otimes$ is the convolution operator. The factor $\alpha = 0.6$ is the empirical decorrelation length for the Morlet wavelet [3].

Statistical significance of cross-spectral coupling was determined using Monte Carlo methods. The null hypothesis is taken as zero coherence between the data at a determined frequency. The data is modelled with a first order autoregressive process, generating a large ensemble of surrogate data set pairs. The wavelet coherence for each pair is calculated and, finally, the significance level is estimated for the different scale taking into account the values outside the cone of influence.

3. Results

Table 1 gives the total number of episodes of ischemic and the non-ischemic HR-related ST changes obtained from all the 86 recordings of the LTSTDB according to the protocols STA, STB and STC together with the parameters for the best distribution fits. Clearly STA is more sensitive that STB which in turn is more sensitive to STC for both ischemic and non-ischemic events. The empirical distribution of the lengths (λ) of the ischemic episodes (in seconds) most closely mapped to f^{ln}. Note that the distributions were not largely affected by changes in protcol, except for a small shift to a longer tail. In the case of non-ischemic episodes, the distributions best matched f^{gev} and the protocol did lead to large differences.

Table 1. Number of ischemic (N_i) and non-ischemic (N_{ni}) episodes according to each of the three protocols together with parameters for best fits.

	STA	STB	STC
N_i	1052	666	509
μ	5.59	5.87	6.09
σ_n	1.02	0.98	0.91
N_{ni}	360	156	82
μ_l	409.54	223.05	146.54
μ_s	372.81	227.98	133.76
ξ	0.64	0.99	0.96

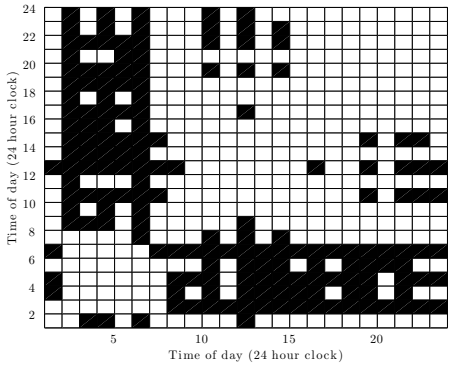

Figure 1. Matrix of p values obtained from the KS test between the HRs at different hours for the ischemic episodes in the case of the protocol STA (a black square indicates significance p<0.05)

A statistical comparison between the ischemic and non-ischemic distributions was then performed for all protocols using the two-sample Kolmogorov-Smirnov test. Distributions were tested with and without extreme values (considered as episodes $>$ 3000 s). All distributions were found to be significantly different (p<0.05).

The magnitude, length and average HR were evaluated as a function of hour of day in which the episode started. Regardless of protocol we observed a diurnal cycle of ischemia with a higher prevalence at 7-8am and 6-7pm and nadirs between these times. Notably the period 12-5am exhibits the fewest ischemic events, which may correspond to subjects being asleep.

A similar pattern was observed for non-ischemic eposides, although the diurnal peaks are not so clear, are delayed with respect to the ischemic peaks, and vary with protocol. The nocturnal drop in events is more highly exaggerated than for ischemic events and may be connected to the noctural drop in HR. No correlation was found between the lengths of the episodes and their starting times for all three protocols and type of episodes (ischemic and non-ischemic).

We found no strong relationship between HR, HRV and length of episode. Again, outliers corresponding to lengths of episodes greater than 3000 s were eliminated and protocols STA, STB and STC exhibited similar behaviour. The KS test was used to test for significant differneces between the HR in ischemic and non-ischemic episodes at matched hour intervals. Statistical significance was considered acceptable at p<0.05. Statistically significant differences in HR exist at 8-9am and generally from 8pm to 5am.

Figure 1 presents the results of a pair-wise KS test applied to the HRs obtained at each hour for the protocol STA for the ischemic episodes. Significance at p $<$ 0.05 is represented by black squares. Note that the upper left (and symmetrically, lower right) quadrant are different to the rest of the data, indicating that night time activity is significantly less frequent than day time activity. In particular, in the case of the ischemic episodes, we can observe a statistically significant difference between the night (1-7am) and day hours. Protocols STB and STC exhibited similar results although with fewer events per hour and the p-values were not significant for as many hour periods.

3.1. Spatial evolution of ischemia

After transformation into the VCG coordinate system, the number of available ischemic episodes was 153 for STA, 80 for STB and 61 for STC. Figure 2 illustrates the evolution of the ST segment over the course of a ischemic episode projected onto the X-axis. Note that the largest ST depression occurred around the J+30 point in the first 100-200 s of this 10 minute episode, which was just when the HR peaked. Figure 3 illsutrates the evolution of the ST elevation across all 12 standard clinical leads. Note that in this case the dominant angle of ischemia appears to move only slightly between the limb and augmented leads. However, we did observed some large jumps in θ and ϕ during the episodes. In general we found that HR, $|V|$, θ and ϕ evolved with a $1/f^{\beta}$ scaling (see Table 2). Note that the ST amplitude ($|V|$) exhibits Brownian like motion ($\beta_{|V|} \approx 2$) and the rest of parameters (θ, ϕ and HR) a mixture of Brown and pink noise. The protocol had only a small effect ($\leq 3\%$) on the ST amplitude, dominant angle and HR behaviour during ischemic episodes.

Table 2. Protocol-dependence of scaling parameter β.

	STA	STB	STC
β_θ	1.57 ± 0.43	1.59 ± 0.35	1.58 ± 0.35
β_ϕ	1.54 ± 0.36	1.55 ± 0.30	1.56 ± 0.31
$\beta_{\|V\|}$	1.78 ± 0.43	1.85 ± 0.40	1.90 ± 0.39
β_{HR}	1.51 ± 0.54	1.52 ± 0.51	1.46 ± 0.53

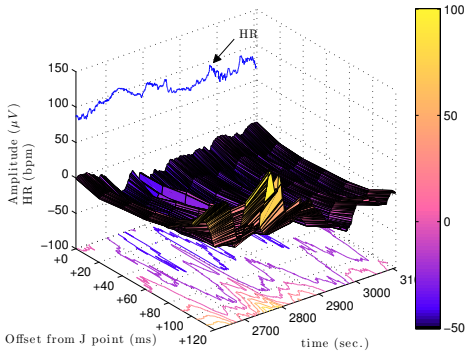

Figure 2. X-axis ST amplitude changes during ischemia

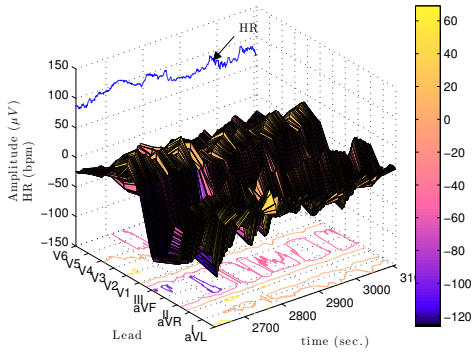

Figure 3. 12 Lead ST amplitude evolution during ischemia

3.1.1. Cross spectral correlation of the HR, angle and ST amplitude

Figure 4 illustrates $C^2_{x,y}(a,\tau)$ between the 4 Hz cubic spline interpolated RR interval and the ST amplitude for a 500 s ischemic episode. Blue indicates little to no coherence and red indicates strong coherence. The black arrows indicate the phase at a given time frequency with vertically upwards: zero phase; pointing right: in-phase; left: anti-phase; down: series1 leading series2 by 90^o. This plot can be interpreted as a significant low frequency coupling ($\sim$ 0.02 Hz to $\sim$ 0.04 Hz) can be observed from 2660 s to 2900 s with a fairly uniform and stationary phase difference of $3\pi/4$ between the ST amplitude and RR interval (reciprocal instantaneous HR). Around 2980 s, there is another period of significant coupling at a slightly higher frequency ($\sim$ 0.03 Hz to $\sim$ 0.06 Hz) for about one minute. Some shorter and higher frequency significant coupling can also be observed from $\sim$ 0.06 Hz to $\sim$ 0.2 Hz for brief 20 s periods around 2800 s and 2870 s into the recording as well as some scattered higher frequency coupling up to the average Nyquist frequency (1 Hz).

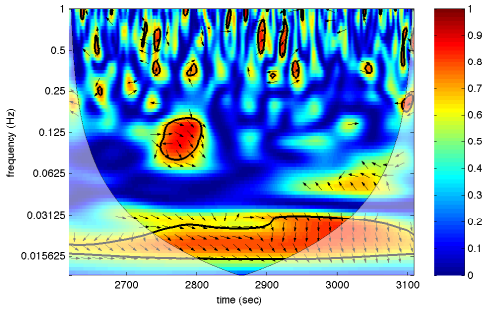

Figure 4. $C^2_{x,y}(a,\tau)$ between θ and HR time series. The 5% significance level against red noise is shown as a thick contour.

4. Conclusions

Our results demonstrate that the evolution of ischemia in the ECG is complex, with changes in HR, dominant angle (θ, ϕ), maximal extent of the ischemic eposiode ($|V|$), and coupling between these parameters over the course of the episode. VLF coupling may be due to activity-related changes or myogenic responses. Coupling at 0.01 Hz may be due to blood pressure or baroflex related changes in HR and ST levels. Coupling at 0.2-0.5 Hz may be due to respiratory artefact changing the position of the heart with respect to ECG lead. Diurnal variations in these parameters, and the length of the episode are also observed. An extended version of this manuscript will be provided to describe a subsequent model.

References

[1] Jager F, Taddei A, Moody G, Emdin M, Antolič G, Dorn R, Smrdel A, Marchesi C, Mark R. Long-term ST database: a reference for the development and evaluation of automated ischaemia detectors and for the study of the dynamics of myocardial ischaemia. Medical and Biological Engineering and Computing 2003;41(2):172–182.

[2] Feild D, Feldman C, et al. Improved EASI coefficients: their derivation, values, and performance. Journal of electrocardiology 2002;35(4):23–33.

[3] Torrence C, Compo G. A practical guide to wavelet analysis. Bulletin of the American Meteorological Society 1998; 79(1):61–78.

[4] Grinsted A, Moore J, Jevrejeva S. Application of the cross wavelet transform and wavelet coherence to geophysical time series. Nonlinear Processes in Geophysics 2004; 11(5/6):561–566.

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