Assessing Instantaneous QT Variability dynamics within a Point-Process Nonlinear Framework

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Abstract—**The importance of cardiac repolarization dynamics in promoting arrhythmic events is widely recognized. To this extent, mathematical modeling and signal processing have played an important role in providing effective measures related to cardiac and autonomic nervous system dynamics. In this study, we introduce an instantaneous assessment of QT variability indices using a point-process nonlinear framework. The analysis includes computation of the dynamical spectrum and bispectrum, as well as time domain features, from data gathered from healthy subjects undergoing a tilt test trial. We demonstrate that an inverse-Gaussian probability function effectively predicts the current QT interval given a nonlinear combination of the past QT intervals modeled through the Laguerre expansion of the Wiener-Volterra terms. Results also show that our approach is able to provide an accurate instantaneous characterization of ventricular repolarization dynamics during changes with posture.**

I. INTRODUCTION

The study of QT variability series refers to the analysis of consecutive temporal intervals gathered from the surface ECG, each of which starts at a Q-wave onset and ends at the consequent T-wave offset. The QT interval reflects the global depolarization and repolarization of the ventricular myocardium under direct control of the autonomic nervous system [1]. Specifically, in healthy subjects, it has been demonstrated that the beat-to-beat fluctuations in QT intervals are mediated by the sympathetic activity [2]. Although several measures that have been proposed in literature are derived from bivariate models of RR and QT variability [3], [4], monovariate QT variability analysis has also been extensively performed using nonlinear methods [1], [2], [5]–[7]. In this study, we propose an instantaneous assessment of QT variability through linear and nonlinear indices gathered from a nonlinear point-process model [8], [9]. This model has been recently developed to study heartbeat dynamics given history dependence on the previous beat intervals. Accordingly, here we investigate the probability density function that predicts the next QT event by testing the Inverse-Gaussian (IG) distribution [10]. From a physiological point-of-view, this choice is motivated by a "Wiener process with drift" model of the rising mechanism of the cardiac membrane potential, where a cardiac contraction begins when a threshold is reached [10]. Moreover, we investigate the role of nonlinear features extracted from the dynamical bispectrum, which can be estimated by using up to second-order nonlinearities of the Wiener-Volterra expansion [8], [9]. The model has been optimized using the discrete-time Laguerre expansions of the Wiener-Volterra autoregressive kernels, allowing for long-term memory and lowest number of parameters to be estimated [8], [9]. Remarkably, the proposed instantaneous assessment can be performed without applying any interpolation method [10].

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II. MATERIALS AND METHODS

The QT Interval Point-Process Nonlinear Model: Details on the proposed point-process nonlinear model have been recently published in [8], [9]. Therefore, here we only describe the specific procedures applied for the novel application on QT variability series. Of note, a QT interval is approximated by the RT interval [3]. Starting from the surface ECG, observed within the interval $t \in (0,T]$, we define $\{u_j\}_{j=1}^J$ as the ordered set of R-wave events and $\{v_j\}_{j=1}^J$ as the ordered set of T-wave events whose fiducial point corresponds to the end of the wave. Then, let $\mathrm{RT}_j = v_j - u_j > 0$, as the j^{th} RT interval. It is also possible to define the counting process $N(t) = \max\{k : u_k \le t\}$ and its differential, $dN(t)$, which is 1 when there is an event (the ventricular contraction), and 0 otherwise. Similarly, a left continuous function $\widetilde{N}(t)$ can be defined as $\widetilde{N}(t) = \lim_{\tau\to t^-} N(\tau) = \max\{k : u_k < t\}$. Assuming history dependence, we use a physiologically-plausible, continuous Inverse-Gaussian distribution $f(t|\mathscr{H}_t, \xi(t))$ as the probability distribution of the waiting time $t-u_j$ until the next RT event appears [8]–[10], with $\xi(t)$ as the parameter vector. To define the first-moment statistic (mean) of the distribution, $\mu_{\mathrm{RT}}(t,\mathscr{H}_t,\xi(t))$, let us consider a Nonlinear Autoregressive with Laguerre expansion (NARL) model :

$$\mu_{\mathrm{RT}}(t,\mathscr{H}_t,\xi(t)) = \mathrm{RT}_{\widetilde{N}(t)} + g_0(t) + \sum_{i=0}^{p} g_1(i,t)\, l_i(k) + \sum_{i=0}^{q}\sum_{j=0}^{q} g_2(i,j,t)\, l_i(k)\, l_j(k)\,. \quad (1)$$

where $l_i(t) = \sum_{n=1}^{\widetilde{N}(t)} \phi_i(n)(\mathrm{RT}_{\widetilde{N}(t)-n} - \mathrm{RT}_{\widetilde{N}(t)-n-1})$ is the output of the Laguerre filters and $\phi_i(n) = \alpha^{\frac{n-i}{2}}(1-\alpha)^{\frac{1}{2}}\sum_{j=0}^{i}(-1)^j\binom{k}{j}\binom{i}{j}\alpha^{i-j}(1-\alpha)^j$ is the i^{th}-order discrete time orthonormal Laguerre function, with $(n \ge 0)$ and α the discrete-time Laguerre parameter. This model corresponds to a traditional nonlinear autoregressive model with second-degree of nonlinearity and infinite long-term memory [8], [9]. We use the Newton-Raphson procedure to maximize the local log-likelihood defined in [8],

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[10] to estimate the unknown time-varying parameter set $\xi(t) = [\xi_0(t), g_0(t), g_1(0,t), ..., g_1(p,t), g_2(0,0,t), ..., g_2(i,j,t)]$ with $\xi_0(t)$ the IG parameter. Each model goodness-of-fit is evaluated by Kolmogorov-Smirnov (KS) distance and autocorrelation plot [10]. Once the model's parameters are derived the instantaneous autospectrum and bispectrum are calculated [8], [9]. Spectral powers are computed by integrating the spectra in the VLF [0.01-0.05 Hz], LF [0.05-0.15 Hz] and HF [0.15-0.4 Hz] ranges. The nonlinear autonomic nervous system interactions are evaluated by integrating the bispectra in each frequency band [8], [9] obtaining Low-Low (LL), Low-High (LH), and High-High (HH) frequency measures.

Experimental Protocol and Statistical Analysis: We estimated instantaneous RT variability indices in a study of 15 healthy subjects performing a head-up tilt table test [11], [12]. Automatic algorithms for R-wave and T-wave detection were applied as described in [13]. Each series is comprised of an initial phase in supine position (4 minutes), followed by a head-up tilt at 70^o lasting for 5 minutes. In order to avoid the transition between the two phases, although all features are calculated instantaneously with a 5 ms of temporal resolution, the statistical analysis considered averaged values over 2 minutes of each phase. These indices include the first and second order moments of the IG distribution, μ_{RT} and σ_{RT}, respectively, the LF and HF power from the dynamical autospectrum along with their ratio, and LL, HH, and LH from the dynamical bispectrum [8], [9]. The model orders $p = 4$, $q = 2$, and $\alpha = 0.2$ were chosen by preliminary KS plots goodness-of-fit analysis [10]. For each index, we evaluated the statistical differences between the two phases expressed as p-values from the Wilcoxon non-parametric test for paired data, under the null hypothesis of equal medians.

III. Results

We found that the NARL model always performed a good prediction of the next RT event (more than 97% of the autocorrelation samples were within the boundaries) and low KS distance values (mean: 0.0669; standard deviation: 0.0359). Concerning the model indices, during the tilt phase, a significant decrease was found in μ_{RT} (Rest: 381.9 ± 17.3; Tilt:348.7 ± 9.9 [ms] $p < 10^{-4}$) with respect to the resting phase. On the contrary, a significant increase in the sum of LF and HF power was found in the tilt phase (Rest: 22.5 ± 7.2; Tilt: 33.3 ± 16.3 [a.u.] $p < 0.03$). We also applied the NARL model to the RR series. We confirmed the results reported in the current literature as we found a significant decrease during the tilt phase in μ_{RR} (Rest: 992.9 ± 68.9; Tilt: 770.7 ± 102.1 [ms] $p < 10^{-4}$), σ_{RR} (Rest: 824.6 ± 474.6; Tilt: 565.5 ± 429.37 [ms^2] $p < 0.02$), and HH (Rest: 8.5 ± 7.4; Tilt: 3.0 ± 2.8 [a.u.] $p < 0.005$) with respect to the resting phase. A significant increase was found in the LF/HF ratio (Rest: 1.6 ± 1.1; Tilt: 8.0 ± 6.3 $p < 0.003$).

IV. Conclusion and Discussion

In conclusion, a point-process nonlinear model has been successfully applied to instantaneously characterize the probability function that predicts the next RT interval given a linear and nonlinear combination of the past RT events. The excellent goodness-of-fit found the IG probability function confirms the suitability of the Wiener process with drift model also in the definition of ventricular repolarization time [10]. Accordingly, results showed low values of KS distance associated to the NARL model fit. The results obtained from the application of the NARL model to the RR series confirmed expected changes in the sympatho-vagal balance with tilt. In addition, for the RT series, we found that the spectral indices LF and HF did not show significant exclusive changes related to the head-up tilt, whereas the total power (LF+HF) significantly increased during the tilt, in line with previous findings [1], [2].

Despite the important role played by the LL, LH, and HH bispectral indices on the RR variability assessment [8], [9], we found that these nonlinear indices do not significantly change when estimated on RT variability series during postural changes. These findings suggest that the complex dynamics associated with ventricular repolarization times are significantly different than the ones associated with the sino-atrial pacing, which encourages further investigations considering phase space measures such as the instantaneous dominant Lyapunov exponent [14], [15]. Future work will also focus on the development of multivariate linear and nonlinear point-process models (as [16]) to study RR-QT interactions.

References

[1] M. Baumert *et al.*, "Relation between QT interval variability and cardiac sympathetic activity in hypertension," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 300, no. 4, pp. H1412–H1417, 2011.

[2] V. Yeragani *et al.*, "Effect of posture and isoproterenol on beat-to-beat heart rate and QT variability," *Neuropsychobiology*, vol. 41, no. 3, pp. 113–123, 2000.

[3] A. Porta *et al.*, "Quantifying electrocardiogram RT-RR variability interactions," *Medical and Biological Engineering and Computing*, vol. 36, no. 1, pp. 27–34, 1998.

[4] R. Almeida *et al.*, "QT variability and HRV interactions in ECG: Quantification and reliability," *IEEE Trans. Biomed. Eng.*, vol. 53, no. 7, pp. 1317–1329, 2006.

[5] R. Berger *et al.*, "Beat-to-beat QT interval variability novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy," *Circulation*, vol. 96, no. 5, pp. 1557–1565, 1997.

[6] K. Bär *et al.*, "Acute psychosis leads to increased QT variability in patients suffering from schizophrenia," *Schizophrenia research*, vol. 95, no. 1, pp. 115–123, 2007.

[7] V. K. Yeragani and K. Radhakrishna Rao, "Nonlinear measures of QT interval series: novel indices of cardiac repolarization lability: Medqthr and lleqthr," *Psychiatry research*, vol. 117, no. 2, pp. 177–190, 2003.

[8] G. Valenza *et al.*, "Point-process nonlinear models with laguerre and volterra expansions: Instantaneous assessment of heartbeat dynamics," *Signal Processing, IEEE Transactions On*, vol. 61, no. 11, pp. 2914–2926, 2013.

[9] ——, "Using laguerre expansion within point-process models of heartbeat dynamics: A comparative study," in *Proc. of EMBC*. IEEE, 2012, pp. 29–32.

[10] R. Barbieri *et al.*, "A point-process model of human heartbeat intervals: new definitions of heart rate and heart rate variability," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 288, no. 1, p. H424, 2005.

[11] M. Orini *et al.*, "Assessment of the dynamic interactions between heart rate and arterial pressure by the cross time–frequency analysis," *Physiological measurement*, vol. 33, no. 3, p. 315, 2012.

[12] ——, "A multivariate time-frequency method to characterize the influence of respiration over heart period and arterial pressure," *EURASIP Journal on Advances in Signal Processing*, vol. 2012, no. 1, pp. 1–17, 2012.

[13] J. P. Martinez *et al.*, "A wavelet-based ECG delineator: Evaluation on standard databases," *IEEE Trans. Biomed. Eng.*, vol. 51, no. 4, pp. 570–581, 2004.

[14] G. Valenza *et al.*, "Instantaneous nonlinear assessment of complex cardiovascular dynamics by laguerre-volterra point process models," in *Proc. of EMBC*. IEEE, 2013, pp. 6131–6134.

[15] L. Citi *et al.*, "Instantaneous estimation of high-order nonlinear heartbeat dynamics by lyapunov exponents," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*. IEEE, 2012, pp. 13–16.

[16] M. Orini *et al.*, "Tetravariate point-process model for the continuous characterization of cardiovascular-respiratory dynamics during passive postural changes," in *Computing in Cardiology (CinC), 2012*. IEEE, 2012, pp. 273–276.