Filtering Approach Based on Empirical Mode Decomposition Improves the Assessment of Short Scale Complexity in Long QT Syndrome Type 1 Population

Vlasta Bari, Andrea Marchi, Giulia Girardengo, Alfred L. George Jr, Paul A. Brink, Sergio Cerutti, *IEEE Fellow*, Lia Crotti, Peter J. Schwartz, and Alberto Porta, *IEEE Member*

Abstract— **This study assesses the complexity of heart period (HP) and QT variability series through sample entropy (SampEn) in long QT syndrome type 1 individuals. In order to improve signal-to-noise ratio SampEn was evaluated over the original series ($SampEn_0$) and over the residual computed by subtracting the first oscillatory mode identified by empirical mode decomposition ($SampEn_{EMD1R}$). HP and QT interval were continuously extracted during daytime (2:00-6:00 PM) from 24 hour Holter recordings in 14 non mutation carriers (NMCs) and 34 mutation carriers (MCs) subdivided in 11 asymptomatic (ASYMP) and 23 symptomatic (SYMP). Both NMCs and MCs belonged to the same family line. While $SampEn_0$ did not show differences among the three groups, $SampEn_{EMD1R}$ assessed over the QT series significantly decreased in ASYMP subjects. $SampEn_{EMD1R}$ identified a possible factor (i.e. the lower short scale QT complexity) that might contribute to the different risk profile of the ASYMP group.**

I. Introduction

Patients affected by long QT syndrome (LQTS) are characterized by a longer ventricular repolarization, condition that can lead to major cardiac events, as torsades de points, ventricular fibrillation and sudden death [1]. The most popular LQTS is the LQTS type 1 (LQT1) involving a mutation on gene KCNQ1 that affects the delayed rectifier potassium current I_{Ks}. LQT1 patients are more likely to show up symptoms in situations characterized by a high sympathetic drive, such as physical and emotional stress and during daytime. Consequently, beta-blockers are the golden standard therapy for this pathology. Although the genetic modification is well known, the phenotypic manifestation of this pathology can be profoundly different among patients with the same mutation. For example patients carrying the mutation can even exhibit no symptoms. Differentiating LQT1 patients in asymptomatic (ASYMP) and symptomatic (SYMP) subjects is a very important clinical challenge because it might lead to a better understanding of the physio-pathological mechanisms underlying the different phenotypes [2]. In this variety of situations, the availability of 24 hour Holter recordings from a founder population [3,4], whose member are all descendants from the same couple originally settled in South Africa in 1690 and composed by mutation carriers (MCs) divided in ASYMP and SYMP subjects and non mutation carriers (NMCs), provides a great opportunity to investigate the factors leading to completely different risk profiles.

Several studies have shown how the variability of the heart period (HP) series is linked to the vagal influences on the sinus node [5], while QT variability carries important information on the sympathetic modulations directed to ventricles [6]. In a previous work we showed that a multiscale complexity analysis based on refined multiscale entropy of HP and QT variability series was useful in differentiating SYMP from ASYMP individuals in LQT1 population [7] especially at long time scales, while at the short time scale the groups can be hardly differentiated. We hypothesized that the QT series derived from 24 hour Holter recordings with low temporal resolution had an unfavorable signal-to-noise ratio preventing the separation among ASYMP and SYMP groups at short time scales [7]. Conversely, at long time scales the effect of low pass filtering procedure canceling fast temporal scales reduced the effect of the noise favoring the differentiation [7].

Empirical mode decomposition (EMD) is a technique identifying signal components (i.e. the intrinsic mode functions, IMFs) at different time scales [8]. Each IMF is characterized by a given central frequency from the fastest to the slowest one. We hypothesized that the fastest IMF calculated from HP and QT series can capture the high frequency, broad band noise due to jitters in the detection of the fiducial points (i.e. the positions of the QRS apex and T-wave end) largely responsible for the low signal-to-noise

This work was supported by Telethon GGP07016 and GGP09247 grants to L.C., P.J.S. and A.P. and by the National Institutes of Health grant HL068880 to A.L.G. and P.J.S.

V. Bari, A. Marchi and S. Cerutti are with Department of Electronics Information and Bioengineering, Politecnico di Milano, Milan, Italy (emails: vlasta.bari@polimi.it, andrea.marchi@polimi.it, and sergio.cerutti@polimi.it).

G. Girardengo and P.J. Schwartz are with Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Centro Diagnostico San Carlo, Milan, Italy (emails: giuliagira82@yahoo.it and peter.schwartz@unipv.it).

A.L. George Jr. is with Department of Medicine and Pharmacology, Vanderbilt University, Nashville, Tennesse, USA (email: al.george@vanderbilt.edu).

P.A. Brink is with Department of Internal Medicine, University of Stellenbosch, Stellenbosch, South Africa (email: pab@sun.ac.za).

L. Crotti is with Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Centro Diagnostico San Carlo, Milan, Italy and Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany (email: liacrotti@yahoo.it).

A. Porta is with Department of Biomedical Sciences for Health, IRCCS Galeazzi Orthopedic Institute, University of Milan, Milan, Italy (tel: +39 02 50319976; fax: +39 02 50319979; email: alberto.porta@unimi.it).

ratio of the QT series as derived from 24 hour Holter recordings.

The aim of this study is to evaluate the short scale complexity of HP and QT variability series derived from 24 hour Holter recordings in LQT1 subjects. The assessment of short scale complexity will be carried out by computing sample entropy (SampEn) over the original unfiltered series ($SampEn_0$) and over the first residual obtained by removing from the original series the fastest IMF estimated via EMD ($SampEn_{EMD1R}$). MC groups was subdivided into SYMP and ASYMP subgroups to check whether the proposed EMD-based filtering approach is helpful to distinguish among groups and can improve risk stratification.

II. Methods

A. Filtering Approach Based on EMD

Given the time series x={x(i), i=1,…,N}, where i is a progressive sample counter and N is the series length, EMD is a technique allowing to decompose the signal into IMFs that are characterized by the following properties: i) symmetry with respect to zero; ii) unique local frequency; iii) different modes do not share the same frequency at the same time [8]. The method is based on an iterative procedure composed by several steps: 1) identification of all the extrema (maxima and minima) of the x series; 2) generation of the upper and lower envelope of x via cubic spline interpolation among all the maxima and minima of x respectively; 3) point-by-point averaging of the two envelopes to compute the local mean series (i.e. m); 4) subtraction of m from x to obtain a mode candidate h [i.e. h(i)=x(i)–m(i)]; 5) if h did not satisfy the previously defined properties necessary to be a IMF, x was replaced with h and the procedure was repeated starting from the step 1; 6) if h did fulfill the previously defined properties to be a IMF the procedure was repeated starting again from the step 1 over the residual (i.e. the difference between x and all the identified IMFs). The process ended when the amplitude of the residual r satisfied a predefined stopping criterion (i.e., r was below a predetermined level, or r had a monotonic trend) [8]. In this work we identified only the first IMF (i.e. the one with the fastest central frequency) utilized in the filtering procedure.

B. SampEn

Given x we define as a pattern of length L the ordered sequence of L delayed samples, $x_L(i)=[x(i),x(i-1),\ldots, x(i-L+1)]$. The pattern $x_L(i)$ is actually a point in the L-dimensional embedding space reconstructed with the technique of the lagged coordinates with delay equal to 1. The pattern $x_L(i)$ can be seen as the sequence formed by the current sample, x(i), and by the sequence of L-1 past samples, $x_{L-1}(i-1)$. Defined as $x_L=\{x_L(i), i=L,\ldots,N\}$ and $x_{L-1}=\{x_{L-1}(i-1), i=L,\ldots,N\}$ the sets of patterns of length L and L-1 respectively, SampEn estimates the conditional probability that two patterns that are similar in x_{L-1} remain similar, within a tolerance r, in x_L [9]. Sample Entropy was calculated with a tolerance of r equal to 0.15 times the standard deviation of x and with an embedding dimension L=3. $SampEn_{0,x}$ was obtained from the original unfiltered x, while $SampEn_{EMD1R,x}$ from the first residual computed after subtracting the first IMF from x.

III. Experimental Protocol and Data Analysis

A. Experimental Protocol and Study Population

Forty-eight 12 lead 24 hour Holter recordings (Mortara Instrument Inc., Milwaukee, WI, USA and Ela Medical, Sorin Group, Arvada, CO, USA) were acquired from 14 NMC subjects (age from 19 to 56, median=36.5; 6 males) and 34 Mutation Carriers divided in 11 ASYMP subjects (age from 24 to 62, median=46; 4 males) and 23 SYMP individuals (age from 16 to 57, median=39; 9 males). Sampling rate was 180 Hz for Mortara and 200 Hz for Ela Medical recordings. The analysis was carried out on lead with the best signal-to-noise ratio. Subjects did not take any drugs before the study, including beta-blockers. All subjects and/or family members provided written informed consent. The study is in keeping with the principles of the Declaration of Helsinki for medical research involving human subjects. The human research and ethical review boards of the Universities of Stellenbosch, Vanderbilt and Pavia.

B. Series Extraction

We computed HP as the temporal distance between two consecutive R peaks of the ECG. Jitters in the QRS location were minimized via parabolic interpolation. Then, we took the time distance between R peak and the end of the T-wave as an approximation of the QT interval [10]. The end of the T-wave was located when the first derivative over the descending part of the T-wave went below a user-defined threshold computed as 0.3 times the maximum value of the first derivative computed on the T-wave downslope. HP and QT interval were automatically extracted from Holter recordings. Results were manually checked to avoid missing beats or erroneous identifications. HP and QT series were corrected through cubic spline interpolation only in case of missing beats, detection of spikes of noise or evident arrhythmias. The number of the corrections was always kept

TABLE I
Time Domain Parameters from HP and QT Interval Series in NMC, ASYMP and SYMP Subjects

	NMC	ASYMP	SYMP
μ_{HP} [ms]	697±100	847 ±143§	761±95
σ^2_{HP} [ms^2]	1195±711	1471±1048	1382±1000
μ_{QT} [ms]	317±39	422±51§	408±42§
σ^2_{QT} [ms^2]	186±243	271±212	115±48*
μ_{QTc} [ms·s$^{-0.5}$]	397±72	462±34§	469±33§

μ_{HP} = HP mean; σ^2_{HP} = HP variance; μ_{QT} = QT mean; σ^2_{QT} = QT variance; μ_{QTc} = QTc mean; NMC = non mutation carrier group; ASYMP = asymptomatic group; SYMP = symptomatic group. Results are reported as mean±standard deviation. The symbol § indicates $p<0.05$ versus NMC subjects. The symbol * indicates $p<0.05$ versus ASYMP individuals.

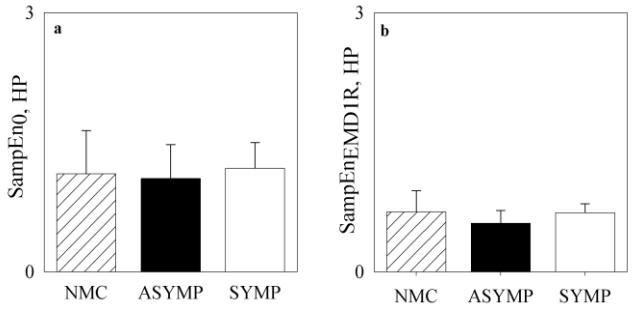

Fig.1. Complexity analysis of HP series over NMC (striped bar), ASYMP (black bar) and SYMP (white bar) subjects. SampEn was computed over the original unfiltered series (a) and over the first EMD residual (b). Values are shown as mean+standard deviation).

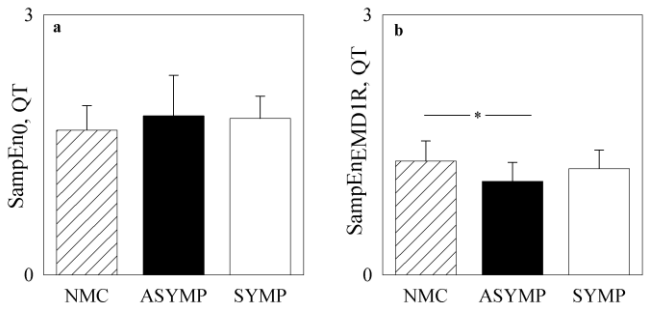

Fig.2. Complexity analysis of QT series over NMC (striped bar), ASYMP (back bar) and SYMP (white bar) subjects. SampEn was computed over the original unfiltered series (a) and over the first EMD residual (b). Values are shown as mean+standard deviation).

below 5% of the duration of the entire series. We calculated the corrected QT (QTc) according to the Bazett's formula (i.e. $QT \cdot HP^{-0.5}$ with QT and HP expressed in ms and s respectively) for each cardiac beat. We considered for each HP and QT series sequences of 5000 consecutive beats and we performed the analysis during daytime (from 2:00 to 6:00 PM). The mean value of the HP, QT and QTc series was calculated and indicated as μ_{HP}, μ_{QT} and μ_{QTc}. The HP and QT series were linearly detrended before calculating variance, indicated as σ^2_{HP} and σ^2_{QT}. Entropy rate indexes were computed from the original unfiltered series (i.e. $SampEn_{0,HP}$ and $SampEn_{0,QT}$) and from the difference between the original series and its first IMF computed via EMD (i.e. $SampEn_{EMD1R,HP}$ and $SampEn_{EMD1R,QT}$).

C. Statistical Analysis

One way analysis of variance (Holm-Sidak test for multiple comparisons), or Kruskal-Wallis one way analysis of variance on ranks (Dunn's method for multiple comparisons) when appropriate, was applied to check the significance of the differences between NMC, ASYMP and SYMP subjects. A $p<0.05$ was always considered as significant.

IV. Results

Table 1 shows the time domain parameters derived from HP, QT and QTc series in NMC, ASYMP and SYMP subjects. ASYMP subjects were characterized by a longer HP interval compared to NMCs. No difference in the HP variance among the three groups was observed. QT and QTc were longer in ASYMP and SYMP subjects with respect to NMCs, reflecting the phenotype of the pathology. Variance of QT series in ASYMP individuals was significantly higher than that of SYMP patients.

Figure 1 shows the results of short scale complexity analysis assessed over HP series in the three groups of subjects. While $SampEn_{0,HP}$ is shown in Fig.1a, $SampEn_{EMD1R,HP}$ is depicted in Fig.1b. Regardless of the series (i.e. unfiltered or EMD HP filtered series) no significant difference in the short scale complexity among the three groups was detected.

Figure 2 shows the results of short scale complexity analysis computed over QT series in the three groups of subjects. While $SampEn_{0,QT}$ is shown in Fig.2a, $SampEn_{EMD1R,QT}$ is depicted in Fig.2b. A significant reduction of the short scale QT complexity in ASYMP subjects compared to NMCs was observable only when SampEn was assessed over the EMD filtered version of the QT series (Fig.2b).

V. Discussion

The main findings of this work can be summarized as follows: i) complexity analysis at fast time scale performed over the original unfiltered HP and QT series did not distinguish the considered groups; ii) the proposed filtering approach based on EMD allowed the limitation of the contribution of the high frequency, broad-band noise on the QT series and the separation among the considered groups; iii) the application of the same approach to the HP series did not produce similar results as a likely consequence of the smaller amount of noise blurring HP dynamics; iv) ASYMP individuals revealed lower complexity of the QT series than NMCs, thus suggesting that having a less complex cardiac control directed to ventricles might be a protective factor against the development of life threatening arrhythmias.

Time domain parameters reflected the phenotype of the pathology, with ASYMP and SYMP subjects showing a longer QT interval with respect to NMC. HP was longer in ASYMP subjects than in NMCs [11,12] and the magnitude of the QT changes was higher in ASYMP group than in SYMP subjects [7]. Both these findings might result in a reduced likelihood in ASYMP subjects to develop arrhythmias because having a longer HP decreases the probability that a new ventricular depolarization encroaches the vulnerable phase of the T-wave [11,12] and featuring higher levels of QT variability, correlated to an higher sympathetic drive [6,13], might be useful to keep under control vagal reactivity [7].

Short scale complexity analysis did not show any difference between groups when calculated over HP series. Since complexity of HP variability is kept high by vagal modulation [14-16], the unaltered value of complexity of HP series suggests that vagal control is active in all the three groups. This conclusion holds also after subtracting the first IMF from the HP series. Indeed, even though the complexity of the HP series significantly decreased, thus indicating that

the first IMF strongly contributed to the complexity of the HP series, the decrease was uniform over the three groups.

Similar results can be obtained when short scale complexity analysis was performed over the original unfiltered QT series. Since complexity of the QT series is kept high by sympathetic control [7], this result supports the conclusion that sympathetic control was similar in all the considered groups. Unfortunately, this conclusion might be the mere consequence of the presence of broad band noise affecting QT measurement especially when performed over 24h Holter recordings with a low temporal resolution such as those present in this historical database [3,4]. The presence of broad band noise might be responsible for the irregularity of the QT series regardless of the actual complexity of the cardiovascular control. Conversely, after the application of the EMD-based filtering approach (i.e. after the subtraction the first IMF from the original QT series), short scale complexity analysis of the QT series was able to differentiate ASYMP from NMC individuals. More specifically, ASYMP subjects exhibited lower complexity than NMC ones, thus suggesting that sympathetic control directed to the ventricles in ASYMP individuals is less complex. This result confirms and extends to short time scales findings detected at longer time scale in [7]. It is remarkable that both QT and QTc suggested similar behavior of the ASYMP and SYMP groups, thus being useless in capturing the different risk profiles associated to the two groups.

VI. Conclusion

We proposed to filter the QT series before assessing its complexity to improve signal-to-noise ratio via an EMD approach. After the application of this filtering procedure we were able to differentiate ASYMP subjects from NMCs, while the same analysis over the original series failed to distinguish the groups. When applied to HP series the same procedure did not produce any remarkable changes in complexity, thus suggesting that HP series was less affected by broad band noise than QT series.

This procedure might be especially helpful for the assessment of the cardiovascular control from QT series because QT variability is characterized by a low signal-to-noise ratio due to the smallness of QT variance and the high degree of indetermination of the T-wave end. However, we suggest the exploitation of this technique on the HP series as well when its variance is very low, thus possibly leading to low signal-to-noise ratios (e.g. in heart failure population, heart transplanted patients or after administration of high dose of atropine in healthy individuals), thus enhancing features of the signal that otherwise might remain unveiled and improve the reliability of the calculation of the HP variability complexity.

References

[1] P.J. Schwartz, S.G. Priori, C. Spazzolini, A.J. Moss, G.M. Vincent, C. Napolitano, I. Denjoy, P. Guicheney, G. Breithardt, M.T. Keating, J.A. Towbin, A.H. Beggs, P. Brink, A.A. Wilde, L. Toivonen, W. Zareba, J.L. Robinson, K.W. Timothy, V. Corfield, D. Wattanasirichaigoon, C. Corbett, W. Haverkamp, E. Schulze-Bahr, M.H. Lehmann, K. Schwartz, P. Coumel, and R. Bloise, "Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias," *Circulation*, vol. 103, pp. 89-95, 2001.

[2] Schwartz PJ, and Crotti L. "QTc behaviour during exercise and genetic testing for the long-QT syndrome," *Circulation*, vol. 124, pp. 2181-2184, 2011.

[3] P.A. Brink, L. Crotti, V. Corfield, A. Goosen, G. Durrheim, P. Hedley, M. Heradien, G. Geldenhuys, E. Vanoli, S. Bacchini, C. Spazzolini, A.L. Lundquist, D.M. Roden, A.L. George Jr, and P.J. Schwartz, "Phenotypic variability and unusual clinical severity of congenital long-QT syndrome in a founder population," *Circulation*, vol. 112, pp. 2602-1610, 2005.

[4] P.A. Brink, and P.J. Schwartz, "Of founder populations, long QT syndrome, and destiny," *Heart Rhythm*, vol. 6, pp. S25-S33, 2009.

[5] S. Akselrod, D. Gordon, F.A. Ubel, D.C. Shannon, R.D. Berger, and R.J. Cohen, "Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control," *Science*, vol. 213, pp. 220-223, 1981.

[6] A. Porta, E. Tobaldini, T. Gnecchi-Ruscone, and N. Montano, "RT variability unrelated to heart period and respiration progressively increases during graded head-up tilt," *Am. J. Physiol.* vol. 298, pp. H1406-H1414, 2010.

[7] V. Bari, J.F. Valencia, M. Vallverdú, G. Girardengo, A. Marchi, T. Bassani, P. Caminal, S. Cerutti, A.L. George Jr, P.A. Brink, L. Crotti, P.J. Schwartz, and A. Porta, "Multiscale complexity analysis of the cardiac control identifies asymptomatic and symptomatic patients in long QT syndrome type 1," *PLoS ONE*, vol. 9, e93808, 2014.

[8] N. E. Huang, Z. Shen, S. R. Long, M. C. Wu, H. H. Shih, Q. Zheng, N. Yen, C. C. Tung, and H. H. Liu, "The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis," *Proc. R. Soc. Math. Phys. Eng. Sci.*, vol. 454, pp. 903-995, 1998.

[9] J.S. Richman and J.R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *Am. J. Physiol.* vol. 278, pp. H2039-H2049, 2000

[10] A. Porta, G. Baselli, F. Lombardi, S. Cerutti, R. Antolini, M. Del Greco, F. Ravelli, and G. Nollo, "Performance assessment of standard algorithms for dynamic R-T interval measurement: comparison between R-Tapex and R-Tend approach," *Med Biol Eng Comput*, vol. 36, pp. 35-42, 1998.

[11] P.J. Schwartz, E. Vanoli, L. Crotti, C. Spazzolini, C. Ferrandi, A. Goosen, P. Hedley, M. Heradien, S. Bacchini, A. Turco, M.T. La Rovere, A. Bartoli, A.L. George Jr, P.A. Brink, "Neural control of heart rate is an arrhythmia risk modifier in long QT syndrome". *J. Am. Coll. Cardiol.,* vol. 51, pp. 920-929, 2008.

[12] L. Crotti, C. Spazzolini, A.P. Porretta, F. Dagradi, E. Taravelli, B. Petracci , A. Vicentini, M. Pedrazzini, M.T. La Rovere, E. Vanoli, A. Goosen, M. Heradien, A.L. George Jr, P.A. Brink and P.J. Schwartz, "Vagal reflexes following an exercise stress test. A simple clinical tool for gene-specific risk stratification in the long QT syndrome". *J. Am. Coll. Cardiol.*, vol. 60, pp. 2515-2524, 2012.

[13] A. Porta A, V. Bari, F. Badilini, E. Tobaldini, T. Gnecchi-Ruscone and N. Montano, "Frequency domain assessment of the coupling strength between ventricular repolarization duration and heart period during graded head-up tilt," *J. Electrocardiol.* vol. 44, pp. 662-668, 2011.

[14] A. Porta, T. Gnecchi-Ruscone, E. Tobaldini, S. Guzzetti, R. Furlan and N. Montano, "Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt," *J. Appl. Physiol.* vol. 103, pp. 1143-1149, 2007.

[15] Z. Turianikova, K. Javorka, M. Baumert, A. Calkovska and M. Javorka, "The effect of orthostatic stress on multiscale entropy of heart rate and blood pressure," *Physiol. Meas.* vol. 32, pp.1425-1437, 2011.

[16] A. Porta, P. Castiglioni, M. di Rienzo, V. Bari, T. Bassani, A. Marchi, A.C.M. Takahashi, E. Tobaldini, N. Montano, A.M. Catai, F. Barbic, R. Furlan, A. Cividjian, and L. Quintin, "Short-term complexity indexes of heart period and systolic arterial pressure variabilities provide complementary information," *J. Appl. Physiol.* vol. 113, pp. 1810-1820, 2012.