Time, Frequency and Information Domain Analysis of Heart Period and QT Variability in Asymptomatic Long QT Syndrome Type 2 Patients

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Abstract— **This study was designed to characterize in time, frequency and information domains heart period (HP) and QT interval variabilities in asymptomatic (ASYMP) long QT syndrome type 2 (LQT2) subjects. HP, approximated as the temporal distance between two consecutive R-wave peaks, and QT, approximated as the temporal distance between the R-wave peak and the T-wave offset, were automatically derived from 24h Holter recordings in 10 ASYMP LQT2 patients and 13 healthy non mutation carriers (NMC) subjects. All analyses were carried out during DAY (from 2 to 6 PM) and NIGHT (from 12 to 4 AM). Mean, variance, spectral power and complexity indices at short, medium and long time scales were assessed over HP and QT beat-to-beat series. Circadian rhythmicity was evident in both NMC and ASYMP LQT2 but ASYMP LQT2 subjects were characterized by higher HP, QT interval and HP variability during both DAY and NIGHT. In addition, multiscale complexity analysis was able to differentiate the groups by showing a higher HP complexity and a lower QT complexity at long time scales in ASYMP LQT2 during DAY. ASYMP LQT2 exhibited a different autonomic control compared to NMC and such a differentiation could be protective and assure them a lower risk profile.**

I. Introduction

Long QT syndrome type 2 (LQT2) is the second main variant of long QT syndrome (LQTS), an inherited disease characterized by an abnormal ventricular repolarization, leading to dramatic events such as syncope, torsades de pointes and sudden death [1]. So far, 13 different genetic mutations leading to LQTS have been identified, all occurring on cardiac ion channels. LQT2 occurs in about 35% of all LQTS patient and it is characterized by a mutation on the human-ether-a-go-go (hERG) gene, encoding the late part of the delayed rectified potassium current, that in normal situation is deputed to prevent early afterdepolarizations [2]. LQT2 symptoms are likely to be triggered by sympathetic activation such as those observed in case of an emotional stress or a stimulus of auditory origin [3]. At difference with the other two most common variants of LQTS, LQTS type-1 (LQT1) and LQTS type-3, whose symptoms occur more likely during daytime and nighttime respectively, the distribution of LQT2 symptoms is less specific over time, with a prevalence at the awakening time, when the alarm rings and patients are suddenly awaked [4]. Furthermore, although LQT1 patients suffer as well from sympathetic driven arrhythmic episodes, the autonomic behavior of LQT1 and LQT2 patients seems to be different. For example, while LQT2 patients were characterized by a sudden increase of corrected QT duration after an epinephrine test, followed by a rapid decrease, the same test provoked a more prolonged increase of the corrected QT in LQT1 subjects [5].

A peculiarity of LQTS is the presence of asymptomatic patients (ASYMP) characterized by the same mutation of symptomatic subjects but that can never develop symptoms during their life. In this study, a patient was defined as ASYMP if he/she never developed symptoms till the age of 20 [6]. So far, several studies have tried to characterize the link between arrhythmias and the state of the autonomic nervous system in LQTS, but this association in ASYMP LQT2 has not been elucidated yet. Heart period (HP) and QT variability analysis in time, frequency and information domains can help to typify the autonomic modulation directed to the heart and ventricles. In particular, the power of HP variability in high frequency band (HF, from 0.15-0.5 Hz) is an index of the parasympathetic control directed to the sinus node [7,8], while the power of QT variability in low frequency band (LF, from 0.04 to 0.15 Hz) is a marker of the sympathetic modulation directed to the ventricles [9,10]. Such indices were recently shown able to characterize autonomic control in LQT1 patients [6]. Furthermore, HP and QT variabilities are characterized by nonlinear features that can be investigated via complexity analysis in the information domain. Entropy rate can quantify the information content of a time series, distinguishing more regular series, with a certain degree of predictability, from

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more complex and unpredictable ones. HP and QT series are also characterized by several temporal scales, being HF and LF the most relevant ones. Consequently, a single-scale complexity analysis could be reductive and a multiscale approach is necessary to characterize the overall complexity of the cardiac control. Recently, a refined multiscale entropy (RMSE) analysis, originally proposed by Costa and lately refined [11,12], was shown able to give important information on vagal and sympathetic control in LQT1 patients [13]. In this work, time and frequency domain markers, together with a refined multiscale complexity analysis were computed from HP and QT variability as derived from 24 Holter recordings of ASYMP LQT2 patients contrasted to non mutation carriers (NMC) subjects, during daytime (DAY) and nighttime (NIGHT) to typify autonomic control of this peculiar group of LQT2 patients.

II. Methods

A. RMSE

Given a time series x of length N, the multiscale entropy (MSE) analysis consists in three steps: i) filtering the series to eliminate the fast temporal scales, ii) undersampling the filtered series, thus reducing its length from N to N\τ at each time scale τ, iii) assessing complexity through sample entropy (SampEn) [14]. The original method [11] filtered the series with a finite impulse response filter with τ coefficients, which cannot prevent aliasing during downsampling. For this reason, the RMSE substitutes the original filter with a 6th order Butterworth filter, avoiding aliasing during downsampling and having a flat response in the pass band. The second refinement of the RMSE is related to the updating of the tolerance *r* for the calculation of SampEn with τ, avoiding the risk that two patterns become undistinguishable solely due to a reduction of the variance of the series due to filtering. We make reference to [12] for a more complete assessment of RMSE. SampEn [14] assesses the conditional probability that two patterns that were close in the embedding space with dimension L-1 remain nearby, within a tolerance *r*, in the L-dimensional space. In this work L was set equal to 3, the time shift between samples was equal to 1 and $r=0.15\cdot SD[x_\tau]$, where x_τ is the filtered downsampled series at scale τ [13].

B. Scale Pooling Procedure

RMSE was computed with τ ranging from 1 to 12. Then, a scale pooling procedure was applied, according to [13], in order to group results in three classes: short time scale with τ=1, medium time scale with τ=2-4 and long time scale with τ=5-12. RMSE at short time scale was equal to assess complexity of the original series, thus taking into account all the time scales present in the short-term variability (i.e. from 0 to 0.5 Hz). The application of the low-pass Butterworth filter with a cutoff of 0.5/τ cycles/sample at medium time scale reduces the superior limit of the pass-band from 0.25 (τ=2) to 0.125 Hz (τ=4) with an HP = 1 s, gradually filtering contributions in the HF band, in addition to those at the highest frequencies, and leaving intact fluctuations in the LF band. At long time scale low-pass filtering approach reduces the superior limit of the pass-band from 0.1 (τ=5) to 0.042 Hz (τ=12), progressively canceling contributions in LF band,

TABLE I
TIME AND FREQUENCY DOMAIN INDICES FROM HP AND QT SERIES IN NMC AND ASYMP LQT2 SUBJECTS DURING DAY AND NIGHT

Parameter	DAY NMC	DAY ASYMP LQT2	NIGHT NMC	NIGHT ASYMP LQT2
μ_{HP} [ms]	696±107	894±102§	896±142*	1086±129*§
σ^2_{HP} [ms^2]	1238±715	3205±2389§	2303±2074	4612±3156§
μ_{QT} [ms]	315±41	383±26§	360±31*	422±35*§
σ^2_{QT} [ms^2]	223±359	93±75	91±89	84±43
HFa_{HP}[ms^2]	102±79	388±339	611±801*	976±950*
LFa_{QT} [ms^2]	26±34	19±18	17±18	16±9

μ_{HP}=HP mean; σ^2_{HP}=HP variance; μ_{QT}=QT mean; σ^2_{QT}=QT variance; HFa_{HP}=power of HP in HF band; LFa_{QT}=power of QT in LF band; NMC = non-mutation carriers; ASYMP LQT2 = asymptomatic long QT syndrome type-2 subjects; DAY=daytime; NIGHT=nighttime. Results are reported as mean±standard deviation. The symbol * indicates $p<0.05$ versus DAY; the symbol § indicates $p<0.05$ versus NMC.

in addition to those in the HF band and at highest frequencies, and leaving intact fluctuations slower than LF band. Values of RMSE were averaged over the three classes (i.e. short, medium and long time scale), and labeled as $RMSE_{\tau=1}$, $RMSE_{\tau=2\text{-}4}$, $RMSE_{\tau=5\text{-}12}$.

C. Autoregressive Spectral Analysis

Parametric spectral analysis was assessed by fitting the series through an autoregressive model, whose optimum model order was defined via the Akaike information criterion [15]. The power spectrum was factorized into components labeled as LF or HF whether their central frequency was in the LF or HF band. The power of HP series in HF band expressed in absolute units (HFa_{HP}) was taken as index of vagal modulation directed to the sinus node, while the power of QT series in LF band expressed in absolute units (LFa_{QT}) was taken as index of sympathetic modulation directed to the ventricles. Analysis was carried out over sequences of 250 beats and iterated over the entire series with an overlap of 50%. The median of the distribution of each parameter was taken as the representative value for the entire series [16].

III. Experimental Protocol and Data Analysis

A. Study Population

Twenty three 12 leads 24h Holter recordings (Mortara Instrument Inc., Milwaukee, WI, USA) were acquired from 10 ASYMP LQT2 patients (age from 20 to 63, median 40, 9 males) and 13 NMC subjects (age from 19 to 56, median 37, 5 males). Subjects did not take any medication, included beta-blockers, the golden standard therapy for LQTS, at the moment of recording. Sampling rate was 180 Hz. The analysis was carried out on the lead characterized by the best signal-to-noise ratio. All subjects provided written informed consent for the study. The ethical review board of IRCCS Istituto Auxologico Italiano and University of Pavia approved the study. The study was performed according to the principles of declaration of Helsinki for medical research involving human subjects.

B. Beat-to-beat Series Extraction

HP was computed as the time distance between two consecutive R-wave peaks on the ECG, located using minimum jitters through parabolic interpolation. QT interval was approximated as the time distance between the R-wave peak and T-wave end [17]. T-wave offset was detected as the point where the absolute first derivative computed on the T-wave downslope descended below a preset threshold (i.e. the 30% of the maximal absolute first derivative). After having automatically extracted HP and QT interval series, the series were manually checked for ectopic beats or misdetections and eventually corrected through cubic spline interpolation between the closest reliable values. The maximum number of corrected points was kept below the 5% of the entire length of the series. Sequences lasting 5000 consecutive beats were analyzed in each group. Analyses were performed during DAY (from 2 to 6 PM) and NIGHT (from 12 to 4 AM). The mean values of HP and QT were calculated during each period and indicated as μ_{HP} and μ_{QT} respectively and expressed in ms. After having linearly detrended the series, the variance of HP and QT was calculated and indicated as σ^2_{HP} and σ^2_{QT} respectively and expressed in ms^2. Then, HFa_{HP} and LFa_{QT} were assessed via spectral analysis and RMSE indices were calculated at short, medium and long time scale over the detrended series of HP and QT and indicated as $RMSE_{HP,\tau=1}$, $RMSE_{HP,\tau=2\text{-}4}$, $RMSE_{HP,\tau=5\text{-}12}$, $RMSE_{QT,\tau=1}$, $RMSE_{QT,\tau=2\text{-}4}$, $RMSE_{QT,\tau=5\text{-}12}$.

C. *Statistical Analysis*

Two-way analysis of variance (Holm-Sidak test for multiple comparisons) was applied to verify the significance of the difference between NMC and LQT2 during DAY and NIGHT for each time, frequency and information domain index. A $p<0.05$ was always considered as significant.

IV. Results

Table 1 shows time, frequency and information domain parameters derived from HP and QT series. It can be observed that both μ_{HP} and μ_{QT} increased during NIGHT with respect to DAY in both NMC and ASYMP LQT2 groups and they were also significantly higher in ASYMP LQT2 with respect to NMC in both conditions. σ^2_{HP} was higher in ASYMP LQT2 with respect to NMC during both DAY and NIGHT, while HFa_{HP} increased in both NMC and ASYMP LQT2 during NIGHT with respect to DAY, thus indicating that both groups exhibited circadian variations of the autonomic modulation. σ^2_{QT} and LFa_{QT} did not change between groups and conditions even though a tendency towards a decrease in the NMC group during NIGHT is visible.

Figure 1 shows RMSE results at short time scale computed over HP (Fig.1a) and QT (Fig.1b) series. It can be observed that short time scale complexity of HP series in NMC was higher during NIGHT than DAY, and during DAY it was larger in ASYMP LQT2 with respect to NMC, while QT complexity did not change. Figure 2 shows RMSE results at medium and long time scales computed over HP (Figs.2a,c) and QT (Figs.2b,d) series. It can be observed that medium time scale complexity of HP (i.e. τ=2-4) in ASYMP LQT2 during DAY was higher with respect to that of NMC, and decreased during NIGHT. Medium time scale QT complexity did not differ between DAY and NIGHT and was smaller in ASYMP LQT2 with respect to NMC during DAY. Long time scale complexity (i.e. τ=5-12) of HP series during DAY was larger in ASYMP LQT2 with respect to NMC and declined during NIGHT in both populations. Long time scale QT complexity was smaller in ASYMP LQT2 with respect to NMC during DAY and was reduced during NIGHT only in NMC.

V. Discussion

Time domain analysis showed that the circadian rhythm was preserved in ASYMP LQT2: indeed, HP and QT interval increased during NIGHT with larger values of QT in ASYMP LQT2 compared to NMC according to the phenotype. Remarkably, HP is longer in ASYMP LQT2 during both DAY and NIGHT, thus suggesting that having a longer HP is a protective factor in this population. The circadian effect is observable in frequency domain parameters as well: indeed, in both NMC and ASYMP LQT2 HFa_{HP} increased during NIGHT. Remarkably, ASYMP LQT2 individuals were characterized by a higher HP variability with respect to NMC group, independently of the period of recording. This peculiarity suggests that ASYMP LQT2 subjects have a higher vagal modulation and this factor could be protective against lethal arrhythmias. Conversely, QT variability and its contribution in the LF band (i.e. LFa_{QT}) were similar in NMC and ASYMP LQT2 groups. On the contrary, a recent finding indicated that in ASYMP LQT1 subjects sympathetic modulation is higher than in NMCs and this factor seems to be protective in ASYMP LQT1 [6]. Taking all together, we conclude that in the two most common LQTS variants (i.e. LQT1 and LQT2) ASYMP subjects exhibit a completely different autonomic profile that confers them an advantage and reduces their specific arrhythmic risk.

NMC group was characterized by the expected HP complexity circadian trend. Indeed, HP complexity is higher at short time scales during NIGHT compared to DAY and lower at longer time scales [12]. ASYMP LQT2 group was characterized by a higher complexity of HP series during DAY with respect to NMC. Since HP complexity at short time scale is under vagal control [12], this finding points to a higher vagal modulation. This issue differentiates again ASYMP LQT2 subjects from ASYMP LQT1 ones [13]. Medium and long time scale complexity of HP was larger in ASYMP LQT2 individuals with respect to NMC ones, thus further corroborating the higher HP complexity in this group. Remarkably, medium and long time scale complexity of QT

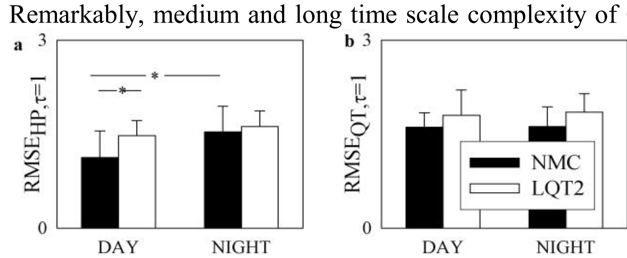

Figure 1. RMSE of HP and QT series at short time scale. RMSE (mean+standard deviation) was assessed in NMC (black bars) and ASYMP LQT2 (white bars) during DAY and NIGHT over HP (a) and QT (b) series. The symbol * indicates $p<0.05$.

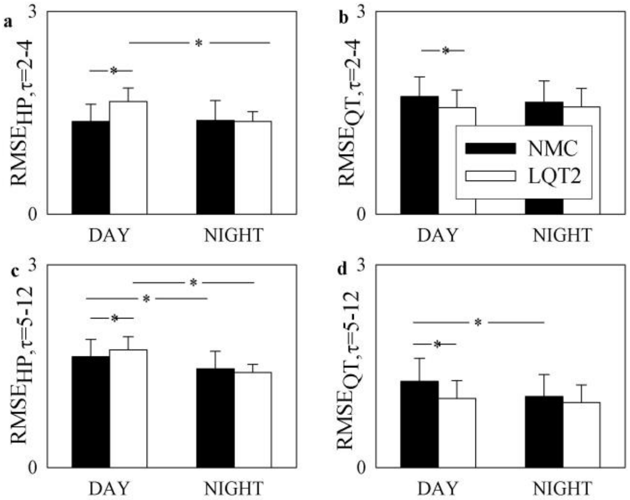

Figure 2. RMSE of HP and QT series at medium (a,b) and long time scale (c,d). RMSE (mean+standard deviation) was assessed over NMC (black bars) and ASYMP LQT2 (white bars) subjects during DAY and NIGHT in HP (a,c) and QT (b,d) series. The symbol * indicates $p<0.05$.

differentiated ASYMP LQT2 from NMC as well, with QT complexity smaller in ASYMP LQT2 than in NMC subjects. Differentiation between ASYMP LQT2 and NMC groups can be achieved only during DAY. The higher complexity of the HP series and the lower complexity of QT series at medium and long time scale are particularly interesting because they suggest some peculiarities of the HP and QT interval control that might play a relevant role in protecting ASYMP LQT2 individuals. Furthermore, RMSE results confirmed the importance of performing multiscale analysis to differentiate LQTS subjects using QT variability derived automatically from 24h Holter recordings [13]. In fact, while at short times scale QT complexity did not differ between groups, at medium and long time scales QT RMSE indices were smaller in ASYMP LQT2 than in NMC individuals.

VI. Conclusions

This study presented a time, frequency and information domain analysis of HP and QT interval variability in ASYMP LQT2 patients contrasted with NMC healthy subjects during DAY and NIGHT. It is a first attempt of evaluating cardiovascular control in ASYMP LQT2 group by exploiting simultaneously HP and QT variability. It emerged that ASYMP LQT2 autonomic regulation is different from that of NMC and that a multiscale complexity analysis unveils peculiarities of the autonomic control that might be fruitfully exploited in LQT2 risk stratification. Further studies comparing ASYMP and symptomatic LQT2 subjects and assessing the effect of beta-blockers are needed in order to better elucidate the link between these findings and the lower risk of ASYMP LQT2 subjects.

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